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Harnan, S. [orcid.org/0000-0002-9318-9206](https://orcid.org/0000-0002-9318-9206), Tappenden, P. [orcid.org/0000-0001-6612-2332](https://orcid.org/0000-0001-6612-2332), Cooper, K. [orcid.org/0000-0002-7702-8103](https://orcid.org/0000-0002-7702-8103) et al. (7 more authors) (2019) Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer: a systematic review and economic analysis. *Health Technology Assessment*, 23 (30). ISSN 1366-5278

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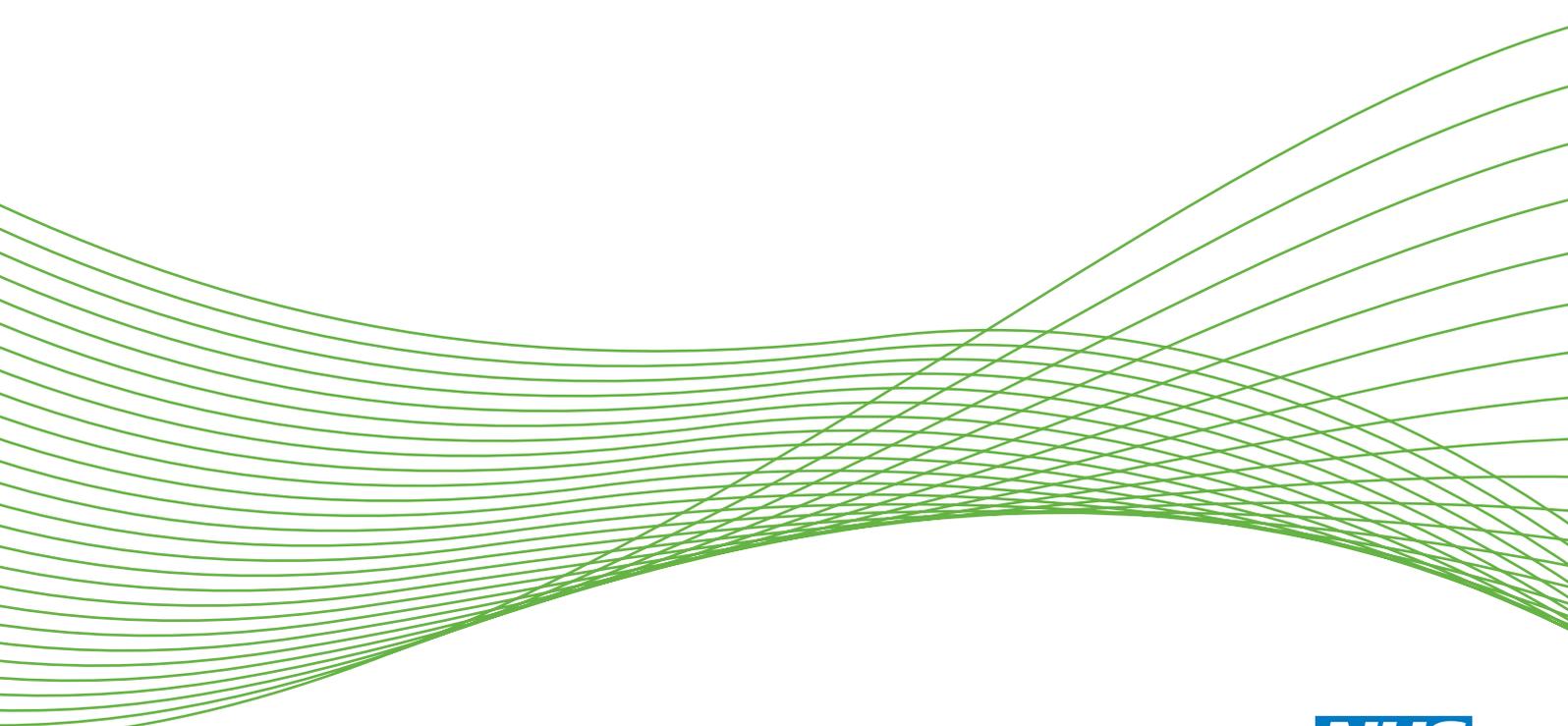
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## Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer: a systematic review and economic analysis

*Sue Harnan, Paul Tappenden, Katy Cooper, John Stevens, Alice Bessey, Rachid Rafia, Sue Ward, Ruth Wong, Robert C Stein and Janet Brown*



**National Institute for  
Health Research**



# Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer: a systematic review and economic analysis

Sue Harnan,<sup>1\*</sup> Paul Tappenden,<sup>1</sup> Katy Cooper,<sup>1</sup>  
John Stevens,<sup>1</sup> Alice Bessey,<sup>1</sup> Rachid Rafia,<sup>1</sup>  
Sue Ward,<sup>1</sup> Ruth Wong,<sup>1</sup> Robert C Stein<sup>2,3</sup> and  
Janet Brown<sup>4</sup>

<sup>1</sup>Health Economics and Decision Science, School of Health and Related Research, University of Sheffield, Sheffield, UK

<sup>2</sup>University College London Hospitals Biomedical Research Centre, London, UK

<sup>3</sup>Research Department of Oncology, University College London, London, UK

<sup>4</sup>Department of Oncology and Metabolism, University of Sheffield, Sheffield, UK

\*Corresponding author

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# Abstract

## Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer: a systematic review and economic analysis

Sue Harnan,<sup>1\*</sup> Paul Tappenden,<sup>1</sup> Katy Cooper,<sup>1</sup> John Stevens,<sup>1</sup> Alice Bessey,<sup>1</sup> Rachid Rafia,<sup>1</sup> Sue Ward,<sup>1</sup> Ruth Wong,<sup>1</sup> Robert C Stein<sup>2,3</sup> and Janet Brown<sup>4</sup>

<sup>1</sup>Health Economics and Decision Science, School of Health and Related Research, University of Sheffield, Sheffield, UK

<sup>2</sup>University College London Hospitals Biomedical Research Centre, London, UK

<sup>3</sup>Research Department of Oncology, University College London, London, UK

<sup>4</sup>Department of Oncology and Metabolism, University of Sheffield, Sheffield, UK

\*Corresponding author [s.harnan@sheffield.ac.uk](mailto:s.harnan@sheffield.ac.uk)

**Background:** Breast cancer and its treatment can have an impact on health-related quality of life and survival. Tumour profiling tests aim to identify whether or not women need chemotherapy owing to their risk of relapse.

**Objectives:** To conduct a systematic review of the effectiveness and cost-effectiveness of the tumour profiling tests onco<sup>type</sup> DX<sup>®</sup> (Genomic Health, Inc., Redwood City, CA, USA), MammaPrint<sup>®</sup> (Agendia, Inc., Amsterdam, the Netherlands), Prosigna<sup>®</sup> (NanoString Technologies, Inc., Seattle, WA, USA), EndoPredict<sup>®</sup> (Myriad Genetics Ltd, London, UK) and immunohistochemistry 4 (IHC4). To develop a health economic model to assess the cost-effectiveness of these tests compared with clinical tools to guide the use of adjuvant chemotherapy in early-stage breast cancer from the perspective of the NHS and Personal Social Services.

**Design:** A systematic review and health economic analysis were conducted.

**Review methods:** The systematic review was partially an update of a 2013 review. Nine databases were searched in February 2017. The review included studies assessing clinical effectiveness in people with oestrogen receptor-positive, human epidermal growth factor receptor 2-negative, stage I or II cancer with zero to three positive lymph nodes. The economic analysis included a review of existing analyses and the development of a de novo model.

**Results:** A total of 153 studies were identified. Only one completed randomised controlled trial (RCT) using a tumour profiling test in clinical practice was identified: Microarray In Node-negative Disease may Avoid ChemoTherapy (MINDACT) for MammaPrint. Other studies suggest that all the tests can provide information on the risk of relapse; however, results were more varied in lymph node-positive (LN+) patients than in lymph node-negative (LN0) patients. There is limited and varying evidence that onco<sup>type</sup> DX and MammaPrint can predict benefit from chemotherapy. The net change in the percentage of patients with a chemotherapy recommendation or decision pre/post test ranged from an increase of 1% to a decrease of 23% among UK studies and a decrease of 0% to 64% across European studies. The health economic analysis suggests that the incremental cost-effectiveness ratios for the tests versus current practice are broadly favourable for the following scenarios: (1) onco<sup>type</sup> DX, for the LN0 subgroup with a Nottingham Prognostic Index (NPI) of > 3.4 and the one to three positive lymph nodes (LN1–3) subgroup (if a predictive

benefit is assumed); (2) IHC4 plus clinical factors (IHC4+C), for all patient subgroups; (3) Prosigna, for the LN0 subgroup with a NPI of > 3.4 and the LN1–3 subgroup; (4) EndoPredict Clinical, for the LN1–3 subgroup only; and (5) MammaPrint, for no subgroups.

**Limitations:** There was only one completed RCT using a tumour profiling test in clinical practice. Except for *oncotype* DX in the LN0 group with a NPI score of > 3.4 (clinical intermediate risk), evidence surrounding pre- and post-test chemotherapy probabilities is subject to considerable uncertainty. There is uncertainty regarding whether or not *oncotype* DX and MammaPrint are predictive of chemotherapy benefit. The MammaPrint analysis uses a different data source to the other four tests. The Translational substudy of the Arimidex, Tamoxifen, Alone or in Combination (TransATAC) study (used in the economic modelling) has a number of limitations.

**Conclusions:** The review suggests that all the tests can provide prognostic information on the risk of relapse; results were more varied in LN+ patients than in LN0 patients. There is limited and varying evidence that *oncotype* DX and MammaPrint are predictive of chemotherapy benefit. Health economic analyses indicate that some tests may have a favourable cost-effectiveness profile for certain patient subgroups; all estimates are subject to uncertainty. More evidence is needed on the prediction of chemotherapy benefit, long-term impacts and changes in UK pre-/post-chemotherapy decisions.

**Study registration:** This study is registered as PROSPERO CRD42017059561.

**Funding:** The National Institute for Health Research Health Technology Assessment programme.

# Contents

<b>List of tables</b>	<b>xi</b>
<b>List of figures</b>	<b>xvii</b>
<b>List of boxes</b>	<b>xix</b>
<b>List of supplementary material</b>	<b>xxi</b>
<b>List of abbreviations</b>	<b>xxiii</b>
<b>Plain English summary</b>	<b>xxvii</b>
<b>Scientific summary</b>	<b>xxix</b>
<b>Chapter 1 Background and definition of the decision problem</b>	<b>1</b>
Condition and aetiology	1
<i>Aetiology, pathology and prognosis</i>	1
<i>Epidemiology and incidence</i>	3
<i>Significance in terms of ill health (burden of disease)</i>	3
<i>Measurement of disease</i>	3
Current service provision	4
<i>Management of early-stage breast cancer</i>	4
<i>Use of adjuvant chemotherapy</i>	4
<i>Current guidelines</i>	4
Description of technologies under assessment	6
<i>Gene expression profiling tests</i>	7
<i>Immunohistochemical-based tests</i>	7
<i>Summary of tumour profiling tests included in the assessment</i>	7
<i>Current usage of tumour profiling tests in the NHS</i>	11
Description of the decision problem	11
<i>Interventions</i>	11
<i>Comparators</i>	12
<i>Population and important subgroups</i>	12
<i>Outcomes</i>	13
Aims and objectives of the assessment	13
<b>Chapter 2 Clinical evidence</b>	<b>15</b>
Methods	15
<i>Identification of studies</i>	15
<i>Inclusion and exclusion criteria</i>	16
<i>Study selection process</i>	19
<i>Data extraction</i>	19
<i>Quality assessment</i>	20
<i>Data presentation and synthesis</i>	21
Results	21
<i>Quantity of evidence</i>	21
<i>Overview of results</i>	22

Results: oncotype DX	23
<i>Development: oncotype DX</i>	23
<i>Prognostic performance: oncotype DX</i>	24
<i>Chemotherapy benefit: oncotype DX</i>	33
<i>Clinical utility: oncotype DX</i>	41
Results: MammaPrint	46
<i>Development: MammaPrint</i>	46
<i>Prognostic performance: MammaPrint</i>	46
<i>Chemotherapy benefit: MammaPrint</i>	54
<i>Clinical utility: MammaPrint</i>	57
Results: Prosigna	67
<i>Prognostic performance: Prosigna</i>	67
Results: EndoPredict and EndoPredict Clinical	68
<i>Development: EndoPredict and EndoPredict Clinical</i>	68
<i>Prognostic performance: EndoPredict and EndoPredict Clinical</i>	68
Results: IHC4	79
<i>Development and analytic validity: IHC4</i>	79
<i>Prognostic performance: IHC4 and IHC4+C</i>	79
Results: all tests compared with each other	90
Results: decision impact studies	90
<i>Decision impact: study and patient characteristics</i>	90
<i>Decision impact: results</i>	92
<i>Summary and discussion of decision impact studies</i>	98
Anxiety and health-related quality of life	98
<i>Oncotype DX</i>	98
<i>MammaPrint</i>	98
<i>EndoPredict</i>	102
<i>Prosigna</i>	102
<i>Discussion</i>	102
<i>Conclusions</i>	102
Time-to-test results	102
<b>Chapter 3 Cost-effectiveness</b>	<b>103</b>
Independent economic evaluation	103
<i>Scope of the External Assessment Group economic analysis</i>	103
<i>Model structure</i>	105
<i>Evidence sources used to inform the model parameters</i>	107
<i>Methods for model evaluation</i>	117
<i>Model verification and validation</i>	118
<i>Cost-effectiveness results</i>	120
<i>Comparison between the Genomic Health model, the current External Assessment Group model and the previous External Assessment Group model (lymph node negative, clinical intermediate-risk subgroup)</i>	138
Discussion	140
<b>Chapter 4 Discussion and conclusions</b>	<b>145</b>
Statement of principal findings	145
<i>Clinical effectiveness: principal findings</i>	145
<i>Cost-effectiveness: principal findings</i>	146
Strengths and limitations of the assessment	147
<i>Strengths and limitations in the clinical evidence base</i>	147
<i>Strengths and limitations relating to the health economic analysis</i>	148

Uncertainties	149
Generalisability	149
Implications for service provision	149
Suggested research priorities	150
<b>Acknowledgements</b>	<b>151</b>
<b>References</b>	<b>153</b>
<b>Appendix 1</b> Additional tables for <i>Chapter 1</i>	<b>199</b>
<b>Appendix 2</b> Literature search strategies	<b>201</b>
<b>Appendix 3</b> Table of excluded studies with rationale	<b>225</b>
<b>Appendix 4</b> Summary of the clinical review	<b>227</b>
<b>Appendix 5</b> Results: all tests compared with each other	<b>235</b>
<b>Appendix 6</b> Review of existing economic analyses published since National Institute for Health and Care Excellence Diagnostics Guidance 10	<b>279</b>
<b>Appendix 7</b> Review and critical appraisal of economic analyses provided by test manufacturers	<b>291</b>
<b>Appendix 8</b> External Assessment Group model input parameter tables	<b>299</b>
<b>Appendix 9</b> External Assessment Group post-test chemotherapy use survey disseminated to UK Breast Cancer Group members	<b>309</b>
<b>Appendix 10</b> Modelled chemotherapy use with and without tumour profiling tests (External Assessment Group model)	<b>311</b>
<b>Appendix 11</b> External Assessment Group cost-effectiveness acceptability curves	<b>313</b>
<b>Appendix 12</b> Additional economic analyses undertaken after submission of the original External Assessment Group report	<b>321</b>



# List of tables

<b>TABLE 1</b> Summary of technologies included in the assessment	<b>8</b>
<b>TABLE 2</b> The PROBAST quality criteria and scoring	<b>20</b>
<b>TABLE 3</b> Oncotype DX prognostic performance: DRFS, DRFI and DFS	<b>26</b>
<b>TABLE 4</b> Oncotype DX: additional prognostic value over clinicopathological factors or comparator tests	<b>30</b>
<b>TABLE 5</b> Oncotype DX RSPC, discrimination, reclassification and additional prognostic value	<b>34</b>
<b>TABLE 6</b> The prediction of chemotherapy responsiveness by oncotype DX: reanalyses of RCT data	<b>36</b>
<b>TABLE 7</b> The prediction of chemotherapy responsiveness by oncotype DX: observational studies	<b>38</b>
<b>TABLE 8</b> Clinical utility results: oncotype DX	<b>43</b>
<b>TABLE 9</b> Prognostic performance of MammaPrint: DRFS/DRFI	<b>48</b>
<b>TABLE 10</b> Prognostic performance of MammaPrint for patients at high or low clinical risk	<b>51</b>
<b>TABLE 11</b> Additional prognostic value for DRFS/DRFI: MammaPrint	<b>52</b>
<b>TABLE 12</b> Prediction of chemotherapy responsiveness: MammaPrint	<b>56</b>
<b>TABLE 13</b> Clinical utility of MammaPrint (MINDACT)	<b>59</b>
<b>TABLE 14</b> Clinical utility of MammaPrint (RASTER study): DRFI in node-negative patients	<b>62</b>
<b>TABLE 15</b> Clinical utility of MammaPrint (RASTER study): additional prognostic value in node-negative patients	<b>64</b>
<b>TABLE 16</b> Clinical utility of MammaPrint (RASTER study): DRFI in node-positive patients	<b>66</b>
<b>TABLE 17</b> Prognostic performance of Prosigna: DRFS/DRFI	<b>69</b>
<b>TABLE 18</b> Additional prognostic value for DRFI/DRFS: Prosigna	<b>72</b>
<b>TABLE 19</b> Prognostic performance of EndoPredict and EPclin: DRFS/DRFI	<b>75</b>
<b>TABLE 20</b> Additional prognostic value for DRFI/DMFS: EndoPredict and EPclin	<b>77</b>
<b>TABLE 21</b> Characteristics of prognostic studies: IHC4 and IHC4+C	<b>80</b>

<b>TABLE 22</b> Prognostic performance of IHC4: DRFS and DRFI	<b>84</b>
<b>TABLE 23</b> Additional prognostic value, all outcomes: IHC4	<b>85</b>
<b>TABLE 24</b> Prognostic performance of IHC4+C: DRFI	<b>89</b>
<b>TABLE 25</b> Additional prognostic value, all outcomes: IHC4+C	<b>91</b>
<b>TABLE 26</b> Decision impact results: <i>oncotype</i> DX	<b>93</b>
<b>TABLE 27</b> Decision impact results: EndoPredict (EPClin)	<b>95</b>
<b>TABLE 28</b> Decision impact results: IHC4+C	<b>96</b>
<b>TABLE 29</b> Decision impact results: Prosigna	<b>96</b>
<b>TABLE 30</b> Decision impact results: MammaPrint	<b>97</b>
<b>TABLE 31</b> Study and patient characteristics: anxiety and HRQoL	<b>99</b>
<b>TABLE 32</b> Results: anxiety and HRQoL	<b>100</b>
<b>TABLE 33</b> Scope of the EAG economic analysis	<b>103</b>
<b>TABLE 34</b> Evidence sources used in the model	<b>108</b>
<b>TABLE 35</b> Studies available to inform chemotherapy use conditional on test results	<b>112</b>
<b>TABLE 36</b> Distributions used in EAG probabilistic analyses	<b>118</b>
<b>TABLE 37</b> List of DSAs undertaken for each test	<b>119</b>
<b>TABLE 38</b> Central estimates of cost-effectiveness: <i>oncotype</i> DX vs. current practice – probabilistic model	<b>121</b>
<b>TABLE 39</b> Probability of optimality: <i>oncotype</i> DX vs. current practice	<b>121</b>
<b>TABLE 40</b> Deterministic sensitivity analyses: <i>oncotype</i> DX vs. current practice	<b>122</b>
<b>TABLE 41</b> Central estimates of cost-effectiveness: IHC4+C vs. current practice – probabilistic model	<b>125</b>
<b>TABLE 42</b> Probability of optimality: IHC4+C vs. current practice	<b>125</b>
<b>TABLE 43</b> Deterministic sensitivity analyses: IHC4+C vs. current practice	<b>127</b>
<b>TABLE 44</b> Central estimates of cost-effectiveness: Prosigna vs. current practice – probabilistic model	<b>129</b>
<b>TABLE 45</b> Probability of optimality: Prosigna vs. current practice	<b>129</b>
<b>TABLE 46</b> Deterministic sensitivity analyses: Prosigna vs. current practice	<b>130</b>

<b>TABLE 47</b> Central estimates of cost-effectiveness: EPclin vs. current practice – probabilistic model	132
<b>TABLE 48</b> Probability of optimality: EPclin vs. current practice	132
<b>TABLE 49</b> Deterministic sensitivity analyses: EPclin vs. current practice	133
<b>TABLE 50</b> Central estimates of cost-effectiveness: MammaPrint vs. current practice (mAOL) – probabilistic model	135
<b>TABLE 51</b> Probability of optimality: MammaPrint vs. current practice (mAOL)	135
<b>TABLE 52</b> Deterministic sensitivity analyses: MammaPrint vs. current practice (mAOL)	136
<b>TABLE 53</b> Summary of structural assumptions and evidence sources	139
<b>TABLE 54</b> Comparison of ICERs generated using the current EAG model, the previous EAG model and the Genomic Health model (LN0 NPI > 3.4 subgroup)	141
<b>TABLE 55</b> Incidence of breast cancer per 100,000 people in England, by age group and sex (2014)	199
<b>TABLE 56</b> Breast cancer risk prediction tools	199
<b>TABLE 57</b> Summary of risk categorisation and prognostic and predictive (of chemotherapy benefit) ability across tests	228
<b>TABLE 58</b> Characteristics of prognostic studies: multiple tests	236
<b>TABLE 59</b> Quality assessment of prognostic studies: multiple tests	239
<b>TABLE 60</b> Prognostic performance of multiple tests: DRFI/DMFS/DRFS	241
<b>TABLE 61</b> Prognostic performance of multiple tests: OS	246
<b>TABLE 62</b> Additional prognostic value (likelihood ratio $\chi^2$ values): multiple tests	250
<b>TABLE 63</b> Additional prognostic value (C-indices and multivariable analyses): multiple tests	252
<b>TABLE 64</b> Characteristics of microarray studies	258
<b>TABLE 65</b> Microarray results: HRs	262
<b>TABLE 66</b> Microarray results: C-index (AUC) data	267
<b>TABLE 67</b> Microarray results: additional prognostic value	271
<b>TABLE 68</b> Percentage in each risk category and kappa statistics between tests	276
<b>TABLE 69</b> Existing economic evaluations: analytic scope	281

<b>TABLE 70</b> Existing economic evaluations: modelling approach and assumptions regarding predictive benefit and chemotherapy	<b>283</b>
<b>TABLE 71</b> Evidence sources used in the Genomic Health model	<b>293</b>
<b>TABLE 72</b> Risk of distant recurrence and the benefit (RR) of chemotherapy	<b>293</b>
<b>TABLE 73</b> Parameter values in the LN+ analysis	<b>294</b>
<b>TABLE 74</b> Parameter values for MammaPrint, EndoPredict score, EPclin and Prosigna	<b>294</b>
<b>TABLE 75</b> Results of the Genomic Health model: onco <sup>type</sup> DX vs. standard care and other comparator tests	<b>296</b>
<b>TABLE 76</b> Risk classification probabilities using onco <sup>type</sup> DX, Prosigna, IHC4+C and EPclin (TransATAC)	<b>299</b>
<b>TABLE 77</b> Risk classification probabilities using MammaPrint (MINDACT)	<b>299</b>
<b>TABLE 78</b> The 10-year distant recurrence rates by risk classification for onco <sup>type</sup> DX, Prosigna, IHC4+C and EPclin	<b>300</b>
<b>TABLE 79</b> Calculation of 5-year DMFS probabilities by clinical/genomic risk group and chemotherapy use	<b>301</b>
<b>TABLE 80</b> Baseline chemotherapy probabilities by risk group [provided by NCRAS (Dr Kwok Wong, Senior Cancer Analyst, National Cancer Registration and Analysis Service, 28 June 2017)]	<b>302</b>
<b>TABLE 81</b> Summary of post-test chemotherapy probabilities conditional on risk classification	<b>302</b>
<b>TABLE 82</b> Estimates of adjuvant chemotherapy benefit applied in the EAG model	<b>302</b>
<b>TABLE 83</b> Summary of EQ-5D health state valuations in identified studies	<b>303</b>
<b>TABLE 84</b> Health utilities applied in the EAG model	<b>304</b>
<b>TABLE 85</b> Test costs assumed in the EAG analysis	<b>304</b>
<b>TABLE 86</b> Adjuvant chemotherapy costs applied in the EAG model	<b>305</b>
<b>TABLE 87</b> Endocrine therapy costs applied in the EAG model	<b>306</b>
<b>TABLE 88</b> Cusumano <i>et al.</i> post-test chemotherapy probabilities (node negative and node positive)	<b>306</b>
<b>TABLE 89</b> Penault-Llorca <i>et al.</i> post-test chemotherapy probabilities (LN0)	<b>306</b>
<b>TABLE 90</b> Baseline probability of chemotherapy adjusted by onco <sup>type</sup> DX Breast Recurrence Score (LN0, intermediate clinical risk)	<b>306</b>

<b>TABLE 91</b> Risk classification probabilities and 10-year DMFI probabilities for RSPC (from TransATAC analysis)	307
<b>TABLE 92</b> Prosigna risk classification and distant metastases probabilities derived from Gnant and Filipits (LN+)	307
<b>TABLE 93</b> EndoPredict Clinical risk classification and distant metastases probabilities derived from Dubsy <i>et al.</i> (LN+)	307
<b>TABLE 94</b> MammaPrint risk classification and distant metastases probabilities derived from van 't Veer <i>et al.</i> (LN0)	307
<b>TABLE 95</b> Cost-effectiveness of chemotherapy vs. no chemotherapy	321
<b>TABLE 96</b> The QALY shortfall analysis: oncotype DX (prognostic benefit only)	322
<b>TABLE 97</b> The QALY shortfall analysis: oncotype DX (predictive benefit)	322
<b>TABLE 98</b> The QALY shortfall analysis: IHC4+C	323
<b>TABLE 99</b> The QALY shortfall analysis: Prosigna	324
<b>TABLE 100</b> The QALY shortfall analysis: EPclin	324
<b>TABLE 101</b> The QALY shortfall analysis: MammaPrint	325
<b>TABLE 102</b> Hazard ratios for chemotherapy benefit by oncotype DX risk score based on naive indirect comparisons of Study B20, Study B14 and TransATAC	327
<b>TABLE 103</b> Additional analyses of oncotype DX vs. usual practice including chemotherapy benefit based on naive indirect comparisons of Study B20, B14 and TransATAC: LN0, NPI > 3.4 subgroup	327



## List of figures

<b>FIGURE 1</b> Five-year net survival, by age, for women in England: 2009–13	<b>2</b>
<b>FIGURE 2</b> Five-year relative survival, by stage, for women aged 15–99 years in the former Anglia Cancer Network: 2002–6	<b>2</b>
<b>FIGURE 3</b> Diagnosis and management pathway in breast cancer	<b>5</b>
<b>FIGURE 4</b> The PRISMA flow diagram	<b>21</b>
<b>FIGURE 5</b> The EAG model: decision tree component	<b>105</b>
<b>FIGURE 6</b> The EAG model: state-transition model component	<b>106</b>



# List of boxes

**BOX 1** Main issues relating to the Genomic Health model identified by the EAG **297**



# List of supplementary material

**Report Supplementary Material 1** Comparison of TransATAC data with other study data (risk classification and prognosis)

**Report Supplementary Material 2** Narrative synthesis and additional tables from *Chapter 2, Results: oncotype DX*

**Report Supplementary Material 3** Narrative synthesis and additional tables for *Chapter 2, Chemotherapy benefit: oncotype DX and RSPC*

**Report Supplementary Material 4** Narrative synthesis and additional tables for *Chapter 2, Clinical utility: oncotype DX*

**Report Supplementary Material 5** Narrative synthesis and additional tables from *Chapter 2, Results: MammaPrint*

**Report Supplementary Material 6** Narrative synthesis and additional tables for *Chapter 2, Results: Prosigna*

**Report Supplementary Material 7** Narrative synthesis and additional tables for *Chapter 2, Results: Endopredict and EndoPredict Clinical*

**Report Supplementary Material 8** Narrative synthesis and additional tables for *Chapter 2, Development and analytic validity: IHC4*

**Report Supplementary Material 9** Additional tables for *Chapter 2, Results: decision impact studies*

**Report Supplementary Material 10** Microarray data relating to one test only

Supplementary material can be found on the NIHR Journals Library report project page ([www.journalslibrary.nihr.ac.uk/programmes/hta/163003/#/documentation](http://www.journalslibrary.nihr.ac.uk/programmes/hta/163003/#/documentation)).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.



## List of abbreviations

ABCSG	Austrian Breast and Colorectal Cancer Study Group	DRFI	distant recurrence/relapse-free interval
AE	adverse event	DRFS	distant recurrence/relapse-free survival
AiC	academic in confidence	DSA	deterministic sensitivity analysis
AML	acute myeloid leukaemia	EAG	External Assessment Group
AOL	Adjuvant! Online	EBCTCG	Early Breast Cancer Trialists' Collaborative Group
ASCO	American Society of Clinical Oncology	EPclin	EndoPredict Clinical
ATAC	Arimidex, Tamoxifen, Alone or in Combination	EQ-5D	EuroQol 5-Dimensions
AUC	area under the curve	ER	oestrogen receptor
BCS	Edinburgh Breast Conservation Series	ER–	oestrogen receptor negative
BCSS	breast-cancer-specific survival	ER+	oestrogen receptor positive
BNF	<i>British National Formulary</i>	FACT-B	Functional Assessment of Cancer Therapy – Breast cancer
CALGB	Cancer and Leukemia Group B	FACT-G	Functional Assessment of Cancer Therapy – General
cDNA	complementary deoxyribonucleic acid	FFPE	formalin fixed, paraffin embedded
CE	Conformité Européenne	G-CSF	granulocyte colony-stimulating factor
CEAC	cost-effectiveness acceptability curve	GEICAM	Grupo Español de Investigación en Cáncer de Mama
CHF	congestive heart failure	GEO	gene expression omnibus
CI	confidence interval	GEP	gene expression profiling
CLP	clinical linear predictor	HCHS	Hospital and Community Health Service
CRD	Centre for Reviews and Dissemination	<i>HER2</i>	human epidermal growth factor receptor 2
CTS	clinical treatment score	HER2–	human epidermal growth factor receptor 2 negative
DBCg	Danish Breast Cancer Cooperative Group	HER2+	human epidermal growth factor receptor 2 positive
DCIS	ductal carcinoma in situ	HR	hazard ratio
DFS	disease-free survival	HR+	hormone receptor positive
DG	diagnostics guidance	HRQoL	health-related quality of life
DMFI	distant metastasis-free interval		
DMFS	distant metastasis-free survival		
DNA	deoxyribonucleic acid		

## LIST OF ABBREVIATIONS

HTA	Health Technology Assessment	NPI	Nottingham Prognostic Index
ICER	incremental cost-effectiveness ratio	NSABP	National Surgical Adjuvant Breast and Bowel Project
IDFS	invasive disease-free survival	OPTIMA	Optimal Personalised Treatment of early breast cancer using Multi-parameter Analysis
IES	Intergroup Exemestane Study		
IHC	immunohistochemistry	OPTIMA Prelim	Optimal Personalised Treatment of early breast cancer using Multi-parameter Analysis preliminary
IHC4	immunohistochemistry 4		
IHC4+C	immunohistochemistry 4 plus clinical factors		
IPD	individual patient data	OR	odds ratio
ITT	intention to treat	OS	overall survival
LN+	lymph node positive	PAI-1	plasminogen activator inhibitor 1
LN0	lymph node negative	PAM50	Prediction Analysis of Microarray 50
LN0–3	zero to three positive lymph nodes	PAS	Patient Access Scheme
LN1–3	one to three positive lymph nodes	PR	progesterone receptor
		PR+	progesterone receptor positive
LN1micro	one lymph node micrometastasis	PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
LNmicro	lymph node micrometastases		
LYG	life-year gained	PROBAST	Prediction model study Risk Of Bias ASsessment Tool
mAOL	Modified Adjuvant! Online	PSA	probabilistic sensitivity analysis
MDS	myelodysplastic syndromes	PSS	Personal Social Services
MeSH	medical subject heading	pT	pathological tumour stage
MINDACT	Microarray In Node-negative Disease may Avoid ChemoTherapy	QALY	quality-adjusted life-year
mRNA	messenger ribonucleic acid	RASTER	MicroarRAY-prognOSTics-in-breast-cancER
NCBI	National Centre for Biotechnology Information	RCT	randomised controlled trial
NCCN	National Comprehensive Cancer Network	RFI	recurrence/relapse-free interval
NCIC	National Cancer Institute of Canada	RFS	recurrence/relapse-free survival
NCRAS	National Cancer Registration and Analysis Service	RNA	ribonucleic acid
NHS EED	NHS Economic Evaluation Database	ROR	risk of recurrence
NICE	National Institute for Health and Care Excellence	ROR-C	risk of recurrence based on Prediction Analysis of Microarray 50 subtype information plus tumour size

ROR-P	risk of recurrence based on Prediction Analysis of Microarray 50 subtype information plus proliferation score	SEER	Surveillance, Epidemiology, and End Results
		STAI	State–Trait Anxiety Inventory
ROR-PT	risk of recurrence based on Prediction Analysis of Microarray 50 subtype information plus proliferation score plus tumour size	STO-3	Stockholm Tamoxifen-3
		SWOG	Southwest Oncology Group
		TAILORx	Trial Assigning Individualized Options for Treatment (Rx)
ROR-S	risk of recurrence based on Prediction Analysis of Microarray 50 subtype information	TC	docetaxel and cyclophosphamide
		TEAM	Tamoxifen vs Exemestane Adjuvant Multinational
ROR-T	risk of recurrence based on Prediction Analysis of Microarray 50 subtype information plus tumour size	TransATAC	Translational substudy of the Arimidex, Tamoxifen, Alone or in Combination
		TRANSBIG	Translating molecular knowledge into early breast cancer management: building on the BIG (Breast International Group) network for improved treatment tailoring
RR	relative risk		
RSPC	recurrence score–pathology–clinical		
RT-PCR	reverse transcription-polymerase chain reaction	UKBCG	UK Breast Cancer Group
RT-qPCR	reverse transcription-quantitative polymerase chain reaction	uPA	urokinase plasminogen activator
SchHARR	School of Health and Related Research	WSG	West German Study Group
		WSG-AGO-Doc	West German Study Group epirubicine and cyclophosphamide-Doc
SchHARR-TAG	School of Health and Related Research Technology Assessment Group	WTP	willingness to pay
SE	standard error		

## Note

This monograph is based on the Technology Assessment Report produced for NICE. The full report contained a considerable number of data that were deemed confidential. The full report was used by the Appraisal Committee at NICE in their deliberations. The full report with each piece of confidential data removed and replaced by the statement ‘confidential information (or data) removed’ is available on the NICE website: [www.nice.org.uk](http://www.nice.org.uk).

The present monograph presents as full a version of the report as is possible while retaining readability, but some sections, sentences, tables and figures have been removed. Readers should bear in mind that the discussion, conclusions and implications for practice and research are based on all the data considered in the original full NICE report.



## Plain English summary

**B**reast cancer is the most commonly diagnosed cancer in women in England and Wales. Breast cancer, and its treatment, can have an impact on a person's health-related quality of life and survival. Tumour profiling tests are used before chemotherapy. They test small samples of a patient's tumour (removed during surgery) to find out whether the genes in it mean that a person has a high or low risk of the disease returning (relapse). If the risk is low, the patient may be able to avoid having chemotherapy and, therefore, avoid its side effects. Some tests might also be able to identify which patients will respond to chemotherapy.

This study looked at the evidence for five tumour profiling tests. A total of 153 studies were identified. This study considered the results and the quality of the studies to find out if the tests are helpful. Most studies had design flaws (e.g. some patients had already had chemotherapy) that meant that the studies were of low quality overall. The results suggest that all of the tests can give information on the risk of relapse; however, some tests may be less useful in patients whose disease has spread to the lymph nodes (lymph node-positive disease). There was limited and varying evidence about whether or not two of these tests can also predict which patients will respond to chemotherapy.

This study also looked at whether or not these tests represent good value for money for the NHS through cost-effectiveness analyses. The analyses showed that some of the tests may represent a good use of NHS resources for some patient groups; however, there was still a lot of uncertainty about this.



# Scientific summary

## Background

Breast cancer is the most commonly diagnosed cancer in women in England and Wales. In 2014, 55,222 new cases of breast cancer were diagnosed. Treatment usually involves surgery to remove the primary tumour and any involved lymph nodes; this may be followed by radiation therapy, endocrine therapy and/or chemotherapy with or without trastuzumab (Herceptin®, Roche Products Ltd) depending on tumour and patient variables. A proportion of patients also receive neoadjuvant therapy prior to surgery. Although chemotherapy can reduce the likelihood of cancer recurrence and death for women with breast cancer, it may have considerable adverse effects. Improved information on a patient's risk of recurrence (i.e. prognostic risk) and/or likely response to chemotherapy (i.e. predictive benefit) may help target chemotherapy to those patients who will benefit the most. Avoiding chemotherapy in patients at low risk of recurrence, who would therefore obtain limited absolute benefit, avoids the unpleasant side effects of chemotherapy and reduces expenditure on both the chemotherapy itself and the treatment of these adverse effects. Tumour profiling tests aim to improve the use of chemotherapy in breast cancer by improving the categorisation of patients in accordance with risk and the identification of those patients who will gain most benefit from chemotherapy.

## Objectives

The overall aim of the assessment was to address the question 'Do tumour profiling tests used for guiding adjuvant chemotherapy decisions in patients with early-stage breast cancer represent a clinically effective and cost-effective use of NHS resources?'. This includes an update of the systematic review and cost-effectiveness analysis that informed National Institute for Health and Care Excellence (NICE) Diagnostics Guidance (DG) 10.

The objectives of the assessment were to:

- conduct a systematic review of the published evidence on the effectiveness and cost-effectiveness of five tumour profiling tests with or without clinicopathological factors [EndoPredict® (Myriad Genetics Ltd, London, UK), oncotype DX® (Genomic Health, Inc., Redwood City, CA, USA), MammaPrint® (Agendia, Inc., Amsterdam, the Netherlands), immunohistochemistry 4 (IHC4) and Prosigna® (NanoString Technologies, Inc., Seattle, WA, USA)] to guide decisions about adjuvant chemotherapy
- develop a health economic model to assess the cost-effectiveness associated with the use of tumour profiling tests compared with current prognostic tools to guide the use of adjuvant chemotherapy in early-stage breast cancer from the perspective of the NHS and Personal Social Services (PSS).

## Methods

This report was commissioned by the National Institute for Health Research Health Technology Assessment (HTA) programme as project number 16/30/03. A registered protocol of the systematic review (CRD42017059561) is available on the PROSPERO website: [www.crd.york.ac.uk/prospero/display\\_record.asp?ID=CRD42017059561](http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42017059561) (accessed 10 May 2018).

### Clinical evidence review methods

A systematic review was undertaken, which included results from a search of nine databases in February 2017 plus other sources including a review published in 2013. The review included studies assessing clinical effectiveness of the five tumour profiling tests to guide decisions about adjuvant chemotherapy in

people with early-stage breast cancer, with a focus on those with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) stage I or II cancer with zero to three positive lymph nodes. Outcomes included prognostic performance (whether or not recurrence and survival outcomes differ between test risk groups), prediction of chemotherapy benefit (whether or not effect of chemotherapy differs between test risk groups), clinical utility (the impact of prospective use of the test on recurrence and survival) and decision impact (changes in chemotherapy recommendations pre/post test).

### Cost-effectiveness methods

The External Assessment Group (EAG) undertook a review of existing economic analyses published since NICE DG10. The EAG also reviewed and critically appraised economic analyses of *oncotype* DX, MammaPrint and EndoPredict, which were provided during the course of the appraisal.

In addition, the EAG developed a de novo health economic model to assess the cost-effectiveness of *oncotype* DX, MammaPrint, Prosigna, EndoPredict Clinical (EPclin) and IHC4 plus clinical factors (IHC4+C), each compared with current practice. The health economic analysis was undertaken from the perspective of the NHS and PSS and was largely based on the model developed to inform NICE DG10. The EAG model adopts a hybrid decision tree/Markov structure. The model parameters were informed by a number of sources, including a bespoke analysis of the Translational substudy of the Arimidex, Tamoxifen, Alone or in Combination (TransATAC) trial, the Microarray In Node-negative Disease may Avoid ChemoTherapy (MINDACT) trial, a bespoke analysis of the National Cancer Registration and Analysis Service data set, a bespoke survey disseminated by the UK Breast Cancer Group (UKBCG), the NHS England Access Scheme Database, standard costing sources and other literature.

## Results

### Clinical evidence results

The review included 153 studies across all five tests and across all outcomes listed in the NICE scope. Four of these were data sets provided by a company as commercial-in-confidence or academic-in-confidence data and could not be presented in this report.

Among studies of lymph node-negative (LN0) patients receiving endocrine monotherapy, percentages of patients categorised as high risk ranged from 9% to 33% across all five tests. In lymph node-positive (LN+) patients, three tests [Prosigna/ROR-PT (risk of recurrence based on Prediction Analysis of Microarray 50 subtype information plus proliferation score plus tumour size), EPclin and IHC4+C] categorised far more (38% to 76%) LN+ patients than LN0 patients as high risk among studies of endocrine monotherapy, whereas *oncotype* DX categorised a similar number as high risk in the LN0 and LN+ groups. However, *oncotype* DX categorised more patients as low risk in LN+ than other tests (57% in *oncotype* DX vs. 4% to 28% in other tests), but with worse 10-year distant recurrence/relapse-free survival/distant recurrence/relapse-free interval outcomes (82% in *oncotype* DX vs. 95% to 100% in other tests).

In terms of prognostic performance, all tests had statistically significant prognostic power in unadjusted analyses in LN0 and LN+ populations. However, recurrence score-pathology-clinical (RSPC) was only validated in LN0 patients in a cohort that had been used in part to derive *oncotype* DX, and unadjusted analyses using clinical cut-off points were not reported in the validation sets for IHC4 or IHC4+C. All tests provided additional prognostic information in addition to the most commonly used clinicopathological factors and in addition to clinical treatment score and Nottingham Prognostic Index (NPI) in LN0, although data were not reported by risk group for *oncotype* DX. Results were more varied in LN+ patients.

There was some evidence of differential chemotherapy benefit between risk groups for *oncotype* DX, as shown by significant interaction tests between risk group and chemotherapy treatment in unadjusted analyses. Adjusted interaction tests were significant/borderline significant in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B20 study (LN0 patients, significant in HER2- patients), whereas in the

Southwest Oncology Group (SWOG)-8814 (LN+ patients), they were significant when adjusted for some clinicopathological variables individually, but not when adjusting for ER determined by Allred status. However, part of the NSABP B20 cohort was the derivation cohort for *oncotype* DX and this may bias results in favour of observing an interaction. *oncotype* DX RSPC (*oncotype* DX plus age, tumour size and grade) was prognostic but not statistically significantly predictive for chemotherapy benefit and was not tested in an entirely independent validation cohort.

Evidence relating to the ability of MammaPrint to predict benefit from chemotherapy was extremely limited. Although the effect of chemotherapy was significant in high-risk groups and not significant in low-risk groups, interaction tests between risk groups and chemotherapy treatment were not significant, suggesting that there was no statistically significant difference in the effect of chemotherapy between risk groups.

The MINDACT randomised controlled trial (RCT) for MammaPrint was, at the time of writing, the only RCT to have reported (in full) the use of a test in clinical practice compared with clinical practice only. It reported that, for patients with a high Modified Adjuvant! Online (mAOL) score (clinical risk) and a low MammaPrint risk, chemotherapy gave a non-significant absolute benefit of 1.5% in 5-year distant metastasis-free survival (DMFS) ( $p = 0.267$ ). This met the primary objective in that the lower bound of the 95% confidence interval for 5-year DMFS in the no-chemotherapy group was  $\geq 92\%$ . This finding was interpreted by the authors as implying that patients who had a high clinical risk but a low MammaPrint risk could potentially avoid chemotherapy. In patients who were low-mAOL with a high MammaPrint risk, chemotherapy gave an absolute benefit of 0.8%. This could be interpreted to mean that MammaPrint would not be a useful test in mAOL low-risk patients, as it would not alter treatment decisions.

For *oncotype* DX and MammaPrint, evidence from observational, non-comparative studies assessing the impact of the test used prospectively in clinical practice suggested that recurrence/survival outcomes in low-risk groups were acceptable even with low rates of chemotherapy. There was no similar evidence relating to the other tests.

Decision impact studies reported that the percentage of patients with any change in chemotherapy recommendation or decision pre/post test ranged from 27% to 49% across UK studies (these included *oncotype* DX, EndoPredict and IHC4+C) and from 5% to 70% across European studies (these included all tests except IHC4). The net change in the percentage of patients with a chemotherapy recommendation or decision pre/post test ranged from an increase of 1% to a decrease of 23% among UK studies and from a change of 0% to a decrease of 64% across European studies.

Concordance between tests was not fully reviewed as it was not within the scope of the assessment, but one UK study [Optimal Personalised Treatment of early breast cancer using Multi-parameter Analysis preliminary (OPTIMA Prelim)] that compared *oncotype* DX, MammaPrint, Prosigna and IHC4 concluded that although tests assigned similar proportions of patients to low/intermediate- and high-risk categories, test results for an individual patient could differ markedly depending on which test was used.

Data relating to anxiety and health-related quality of life (HRQoL) were limited as most studies did not include a comparator, instead adopting a pre–post test design. Anxiety generally reduced post test, but it is unclear if this would happen equally after a treatment decision made in accordance with clinical factors. HRQoL improved in some analyses.

Microarray studies support conclusions from studies using the commercial versions of the assays in suggesting that *oncotype* DX, MammaPrint and EndoPredict can discriminate between high- and low-risk patients regardless of lymph node status (there were no relevant microarray studies for EndoPredict or IHC4).

### Cost-effectiveness results

The EAG's base-case model suggests the following results.

### Oncotype DX

Within the subgroup of LN0 patients with a NPI of  $\leq 3.4$ , the incremental cost-effectiveness ratio (ICER) for oncotype DX versus current practice is expected to be £122,725 per quality-adjusted life-year (QALY) gained (£34,245 per QALY gained assuming a predictive benefit). Within the subgroup of LN0 patients with a NPI of  $> 3.4$  and the one to three positive lymph nodes (LN1–3) subgroup, oncotype DX is expected to be dominated by current practice (conversely, oncotype DX dominates current practice if a predictive benefit is assumed). The results generated using the EAG model are primarily driven by the modelled reduction in the use of adjuvant chemotherapy using the oncotype DX test. When based on the same evidence sources, the Genomic Health, Inc. (Redwood City, CA, USA) model produces broadly similar results.

### IHC4 plus clinical factors

Within the subgroup of LN0 patients with a NPI of  $\leq 3.4$ , the ICER for IHC4+C versus current practice is expected to be £2654 per QALY gained. Within the subgroup of LN0 patients with a NPI of  $> 3.4$  and the LN1–3 subgroup, IHC4+C is expected to dominate current practice.

### Prosigna

Within the subgroup of LN0 patients with a NPI of  $\leq 3.4$ , the ICER for Prosigna versus current practice is expected to be £91,028 per QALY gained. Within the subgroup of LN0 patients with a NPI of  $> 3.4$  and the LN1–3 subgroup, the ICERs for Prosigna versus current practice are £26,058 and £28,731 per QALY gained, respectively.

### EndoPredict Clinical

Within the subgroup of LN0 patients with a NPI of  $\leq 3.4$ , the ICER for EPclin versus current practice is expected to be £147,419 per QALY gained. Within the subgroup of LN0 patients with a NPI of  $> 3.4$ , the ICER for EPclin versus current practice is expected to be £46,788 per QALY gained. Within the LN1–3 subgroup, the ICER for EPclin versus current practice is expected to be £21,458 per QALY gained.

### MammaPrint

Within the overall MINDACT population, the ICER for MammaPrint versus current practice is expected to be £131,482 per QALY gained. Within the mAOL high-risk subgroup, MammaPrint is expected to be dominated by current practice. Within the mAOL low-risk subgroup, the ICER for MammaPrint versus current practice is expected to be £414,202 per QALY gained.

## Discussion

### *Strengths and limitations in the clinical evidence base*

The evidence base was large but included only one RCT of a test being used in clinical practice compared with usual clinical practice that had reported results in full (MINDACT, for MammaPrint). A number of reanalyses of RCTs, which are generally considered to be high-quality sources of data, were also included in the reviews of prognosis and prediction of chemotherapy benefit. However, nearly all studies excluded patients who did not have enough tissue sample, meaning that patients with small tumours are, in theory, likely to be under-represented.

Many studies were funded by industry and this should be borne in mind when interpreting the evidence base.

Many studies were observational in nature, and these are subject to confounding, whereby exclusion of patients who received chemotherapy is likely to introduce bias as these patients are likely to be systematically different in terms of known (and potentially unknown) prognostic variables. Equally, studies that included patients who received chemotherapy may underestimate prognostic effect.

There were some key gaps in the literature for IHC4+C and RSPC. Notably, IHC4+C and RSPC have only been validated in one cohort each, and this was not entirely independent in the case of RSPC. There are known problems with conducting the analyses required for IHC4, and it is unclear whether or not the absolute IHC4 values obtained would be similar across centres.

Much of the evidence base relates to unadjusted analyses, which do not address the crucial question of whether or not a test has additional value over clinicopathological factors. When adjusted analyses were conducted, the clinicopathological variables included were not always consistent and it is unclear if all important factors were included in all analyses.

There were relatively limited data relating to the ability of *oncoPrint* DX and MammaPrint to predict benefit from chemotherapy, and some of the analyses conducted were also subject to criticisms about adjustment for relevant confounders and use of the derivation cohort. This means that there remains uncertainty about whether or not the tests are associated with a predictive benefit from chemotherapy.

The evidence base relating to the impact of tests on treatment decisions (decision impact studies) was limited in that use of chemotherapy differs across countries and there were no UK studies for two of the tests (MammaPrint and Prosigna) and only one UK study for another two of the tests (EndoPredict and IHC4+C).

### **Strengths and limitations relating to the health economic analysis**

The EAG model has a number of strengths:

- For all tests, risk classification and DMFS probabilities are derived from the same source (TransATAC or MINDACT).
- Within the LNO intermediate-risk subgroup (NPI of > 3.4, analysis of three-level tests), the probability of receiving chemotherapy with and without the test is based on the NHS England Access Scheme Database; this is likely to best reflect how the three-level tumour profiling tests would be used in clinical practice in England.
- The model structure is consistent with that of other published models of tumour profiling tests: when similar data inputs are used, the EAG model produces similar results to the previous EAG model and the Genomic Health model.
- Extensive deterministic sensitivity analyses have been conducted to explore the impact of uncertainty on the model results.

The model is also subject to several limitations, most of which stem from uncertainties in the evidence base. The main limitations and uncertainties relating to the cost-effectiveness analysis are:

- With the exception of *oncoPrint* DX in the subgroup of LNO patients with a NPI of > 3.4 (clinical intermediate risk), the evidence surrounding the pre- and post-test chemotherapy probabilities is subject to considerable uncertainty. This has the propensity to influence the conclusions regarding the cost-effectiveness of all tests.
- There is uncertainty regarding whether or not *oncoPrint* DX and MammaPrint are predictive of chemotherapy benefit; the inclusion of such effects are likely to strongly influence economic conclusions drawn from the analysis.
- The analysis of MammaPrint is based on a different data source to that used in the other four tests.
- The TransATAC study, which was used to estimate test risk classification and DMFS probabilities, was the derivation study for IHC4. For this reason, there is potential for the overestimation of prognostic performance for this test.

## Implications for service provision

The per-test costs for Prosigna provided by NanoString Technologies (used in the EAG economic analyses) are based on an efficient level of throughput. This may not hold if centres do not undertake the anticipated number of tests (e.g. in smaller centres or if multiple tumour profiling tests are available). Furthermore, as NanoString Technologies does not offer a centralised testing service, local testing services will need to be established.

The IHC4 test is not currently commercially available. Standardisation of IHC4 and quality assurance programmes are required before this test may be used routinely within the NHS.

## Suggested research priorities

- There is uncertainty regarding whether or not *oncoType* DX and MammaPrint are predictive of chemotherapy benefit. Further studies that adjust for all relevant clinicopathological factors in validation cohorts are required.
- There is limited evidence demonstrating long-term impacts resulting from the use of the five tumour profiling tests. Future studies assessing the comparative long-term impact of the tests compared with risk prediction tools commonly used in clinical practice would be valuable.
- There is uncertainty regarding the cost-effectiveness of all five tests included in the NICE scope. It is noteworthy that under the assumption of no predictive chemotherapy benefit the inclusion of additional data collected through the NHS England Access Scheme Database has a significant impact on the conclusions previously drawn from the *oncoType* DX analysis within NICE DG10 (moving from an ICER of £22,572 per QALY gained to a situation in which *oncoType* DX is dominated in the subgroup of LNO patients with a NPI of > 3.4). Additional UK-based data collection relating to pre- and post-test chemotherapy use for EPclin, IHC4+C, Prosigna and MammaPrint may be important in reducing existing uncertainty surrounding the cost-effectiveness of these tests.

## Study registration

This study is registered as PROSPERO CRD42017059561.

## Funding

Funding for this study was provided by the HTA programme of the National Institute for Health Research.

# Chapter 1 Background and definition of the decision problem

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## Condition and aetiology

Breast cancer is the most commonly diagnosed cancer in women in England and Wales. In 2014, 55,222 new cases of breast cancer were diagnosed.<sup>2</sup> Treatment usually involves surgery to remove the primary tumour and any involved lymph nodes; this may be followed by radiation therapy, endocrine therapy and/or chemotherapy with or without trastuzumab depending on tumour and patient variables. A proportion of patients also receive neoadjuvant therapy prior to surgery.

## Aetiology, pathology and prognosis

### Aetiology

The causes of breast cancer are not completely understood. A range of risk factors have been identified, including genetic, hormonal and lifestyle factors.<sup>3</sup>

It has been estimated that 12% of women with breast cancer have one affected family member and 1% have two or more affected family members.<sup>4</sup> Genetic predisposition is mediated by high-penetrance genes such as Breast CAncer 1 (*BRCA1*) and Breast CAncer 2 (*BRCA2*), which are responsible for around 80–90% of hereditary cancers, and low-penetrance genes, which confer both increased and decreased risk.<sup>3</sup>

Environmental and lifestyle factors as well as genetic factors influence breast cancer risk. Asian migrants to the West have increased levels of risk compared with the indigenous population, whereas Asian Americans born in the West have incidence rates approximating the US average.<sup>5</sup> Lifestyle and environmental factors thought to increase risk include hormonal factors such as taking the oral contraceptive pill or hormone replacement therapy, higher age of menopause, early age of menarche, late age of first birth and not giving birth. Factors that decrease risk include higher folate intake, higher number of pregnancies, breastfeeding and younger age at first birth.<sup>3</sup> Obesity increases the risk of breast cancer in postmenopausal women.<sup>6</sup> The picture is less clear for premenopausal women, for whom the risk may be lower but prognosis is poorer. Physical activity in adolescence and young adulthood confers a decreased risk of breast cancer,<sup>7</sup> which may be mediated hormonally.

### Pathology

Breast cancer starts with genetic changes in a single cell or a small group of cells in the epithelia of the ducts or the lobules of the breast. The genetic change allows cells to reproduce uncontrollably, resulting in a tumour. Tumours that have not yet spread to surrounding tissue are known as 'carcinoma in situ.' Once it has spread to the surrounding tissue, a tumour is known as 'invasive'. More rapid growth and spread occurs once a blood supply is secured. Cancer spreads via the lymphatic system or the bloodstream. Lymphatic spread is usually first to the axillary lymph nodes. Spread via the bloodstream can lead to distant metastases in the bone or viscera that are incurable.

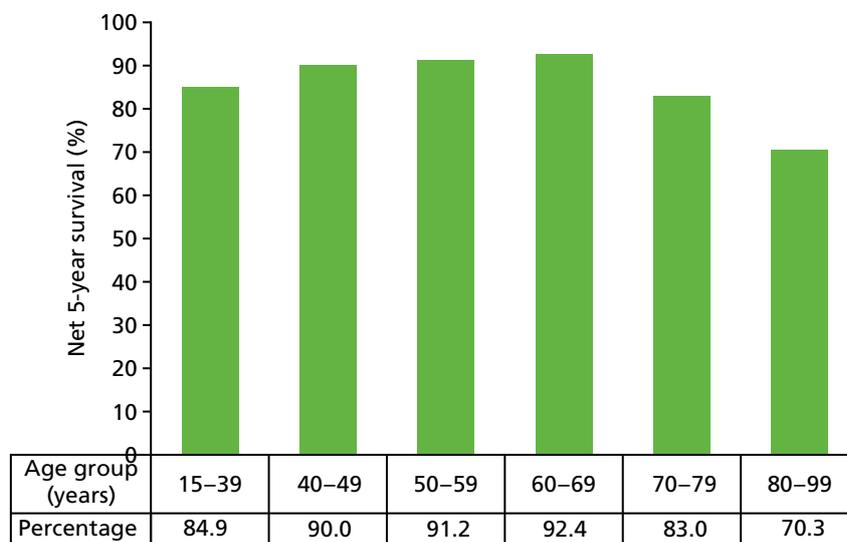
The presence or absence of axillary lymph node metastases is a key indicator of disease and prognosis and adjuvant therapy is, in part, planned based on their presence and extent.<sup>8</sup> They are caused by a single cell or a small number of cells detaching from the main tumour, travelling via the lymphatic system and establishing themselves in the tissue of the axillary lymph nodes. Axillary metastases occur in approximately

41% of cases;<sup>9</sup> prognosis is better when there is no axillary spread. When metastases are present, axillary clearance is indicated in order to prevent further spread and ensure local disease control.

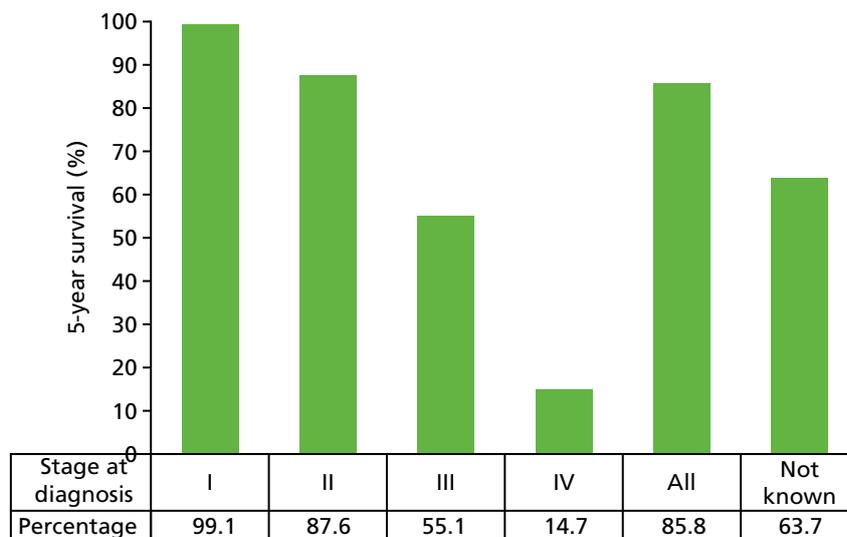
**Prognosis**

Overall, the 5-year, age-standardised survival rate for women with breast cancer is 86.3%.<sup>10</sup> Survival varies with age (*Figure 1*) and stage of disease (*Figure 2*).

Other factors can also affect prognosis. Clinicians may use tools such as the Nottingham Prognostic Index (NPI),<sup>12</sup> Predict (University of Cambridge, Cambridge, UK) or Adjuvant! Online (AOL) (University of Texas Health Sciences Center, San Antonio, TX, USA) to predict disease course and treatment options, although it should be noted that AOL is in the process of being updated and is not currently available. These tools take into account different patient and tumour factors and may give different risk predictions for the same patient.



**FIGURE 1** Five-year net survival, by age, for women in England: 2009–13. Adapted with permission from Cancer Research UK.<sup>11</sup>



**FIGURE 2** Five-year relative survival, by stage, for women aged 15–99 years in the former Anglia Cancer Network: 2002–6. Adapted with permission from Cancer Research UK.<sup>2</sup>

In general, good prognosis is associated with small tumour size, lymph node-negative (LNO) status, younger age, oestrogen receptor positive (ER+) status and progesterone receptor positive (PR+) status. Overexpression of human epidermal growth factor receptor 2 (*HER2*) is associated with poorer prognosis.

### **Epidemiology and incidence**

Incidence varies most in accordance with sex. Women are considerably more likely to develop breast cancer than men. For both sexes, incidence varies with age (see *Appendix 1, Table 55*). Over 81% of cases occur in women aged  $\geq 50$  years. Based on 2014 data, the highest incidence rates for women were reported in those in the 60- to 70-year age group.<sup>13</sup>

Incidence varies with ethnicity. Asian, Chinese and black ethnic groups and those with mixed heritage have a lower incidence of breast cancer than the white ethnic group in England; the rate ratios are 0.65, 0.75, 0.49 and 0.58, respectively, when compared with the white group.<sup>14</sup>

Based on data for the period 2006–10, the incidence of female breast cancer was highest in the least deprived 20% of the population; however, the more deprived group had statistically significantly higher mortality.<sup>15</sup> It is unclear why this is, but may be due to lower levels of screening compliance, worse overall general health status and lower levels of treatment attributable to access and compliance issues.

### **Significance in terms of ill health (burden of disease)**

Breast cancer is the second largest cause of cancer deaths in women, after lung cancer, with an age-standardised mortality rate of 34.6 per 100,000 women. In 2014, breast cancer caused 11,360 deaths of women in the UK.<sup>2</sup>

### **Measurement of disease**

Breast cancer has few obvious symptoms and can easily go undetected for a few years. Among the more noticeable symptoms are a palpable lump in the breast, a change in breast shape and skin appearance or changes to the nipple, such as inversion, a rash or discharge.

A suspicious breast mass may be identified through screening, or via presentation to a general practitioner. Women between the ages of 50 and 70 years are routinely invited to attend regular screening; the NHS is currently in the process of extending the programme as a trial, offering screening to some women aged 47–73 years. A recent case–control study within the NHS England breast screening programme reported that attendance at breast screening resulted in a breast cancer mortality reduction of 39% [odds ratio (OR) 0.61, 95% confidence interval (CI) 0.44 to 0.85] after self-selection correction.<sup>16</sup> Screening increases the proportion of tumours detected in the early, more curable stages.

The breast mass and axillary areas are investigated clinically through palpation and by mammography or ultrasonography, and the status of the tumour is confirmed by histology of a percutaneous tissue biopsy. Staging of the disease depends on tumour size, the number of involved lymph nodes and the presence or absence of distant metastases. Tumour size and axillary metastases can be estimated by clinical examination and imaging techniques, but definitive status is achieved through surgery. Those with small tumours and no axillary metastases have the best prognosis, whereas those with distant metastases are considered incurable. Patients with high-risk early-stage breast cancer also undergo computerised tomography of the chest and abdomen and a bone scan to assess any distant metastases.

### **Current methods for staging of breast cancer**

Three main factors are used to stage breast cancer: (1) tumour size, (2) metastases to the regional lymph nodes and (3) distant metastases. The tumour/node/metastases (TNM) staging system was developed and is maintained by the American Joint Committee on Cancer and the Union for International Cancer Control.<sup>17</sup> The T stage is classified in accordance with the size of the tumour and degree of local infiltration, the N stage is classified in accordance with the number and location of metastases to the lymph nodes in the axilla, between the ribs (internal mammary nodes) and above or below the collarbone (supraclavicular and infraclavicular

nodes), and the M stage is classified by the presence of metastases beyond the breast and regional lymph nodes (see *Table 56, Appendix 1*). Early-stage breast cancer is generally defined as cancer that has not spread beyond the breast or the ipsilateral axillary lymph nodes and is confined to stages I, II or IIIA.

## Current service provision

### *Management of early-stage breast cancer*

Patients diagnosed with early-stage breast cancer currently follow the diagnosis/treatment pathway shown in *Figure 3*.

### *Use of adjuvant chemotherapy*

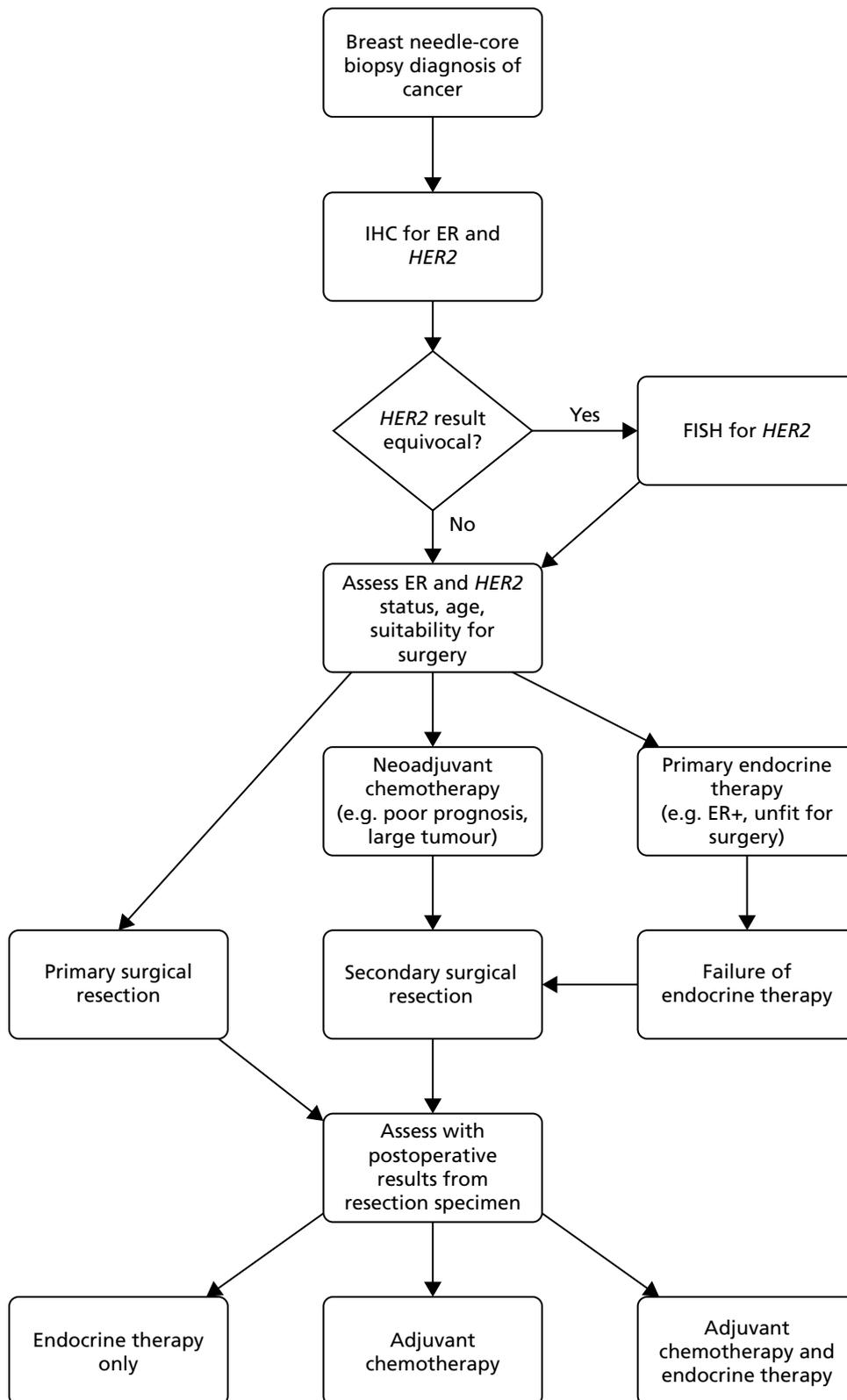
Since 2002, the National Institute for Health and Care Excellence (NICE) has recommended that women at intermediate or high risk of recurrence (ROR) who have not had neoadjuvant chemotherapy should normally be offered a multi-agent chemotherapy that includes anthracyclines.<sup>18</sup> Chemotherapy is defined as the use of cytotoxic medications with the intention of preventing cancer recurrence in patients. It should be noted that, for the purposes of this assessment, chemotherapy does not include other forms of systemic therapy, such as endocrine treatments or targeted biological therapy (e.g. trastuzumab).

Meta-analyses of randomised clinical trials by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) have indicated that the use of adjuvant chemotherapy (chemotherapy following surgery) is associated with a reduction in the risk of cancer recurrence and death in women with early-stage breast cancer.<sup>19</sup> However, chemotherapy is associated with considerable adverse events (AEs). Short- and long-term AEs will affect a proportion of patients receiving chemotherapy, imposing additional costs and reducing health-related quality of life (HRQoL). Short-term AEs that happen during chemotherapy are usually temporary and reversible. The most common AEs include nausea, vomiting, mouth soreness, diarrhoea, tiredness, hair loss and temporary lowering of the blood counts. Long-term AEs, such as damage to the heart, and a small increase in the risk of leukaemia are not reversible. Although chemotherapy may prevent relapse in some, not all women with early-stage breast cancer will benefit and many women remain recurrence-free at 10 years without chemotherapy. However, a subset of patients with a 'good' prognosis may still develop recurrence after curative surgery and adjuvant therapy. This presents a considerable challenge to clinicians in estimating prognosis and making the most appropriate therapeutic decisions relating to whether or not to use adjuvant chemotherapy in women with early-stage breast cancer.

Improved information on a patient's ROR (i.e. prognostic risk) and/or likely response to chemotherapy (i.e. predictive benefit) may help target chemotherapy to those patients who will benefit the most. Avoiding chemotherapy in patients at low ROR, who would therefore obtain limited benefit, avoids the unpleasant side effects of chemotherapy and reduces expenditure on both the chemotherapy itself and the treatment of these adverse effects.

### *Current guidelines*

The NICE Clinical Guideline 80<sup>9</sup> indicates that adjuvant therapy should be considered for all patients with early invasive breast cancer after surgery, based on assessment of the prognostic and predictive factors, the potential benefits and side effects of the treatment. Historically, clinicopathological factors, such as patient age, tumour size, nodal involvement, histological grade, oestrogen receptor (ER) expression, *HER2* overexpression and comorbidities, have been assessed and considered alongside patient preference. The NICE guideline<sup>9</sup> indicates that decisions regarding adjuvant therapy should be made following discussion of these factors with the patient and recommends consideration of the use of AOL to support estimations of individual prognosis and the absolute benefit of adjuvant treatment for patients with early invasive breast cancer. Although there is variation between centres, the NPI and Predict are also commonly used as the basis for many local guidelines on decisions regarding whether or not to use chemotherapy for patients with early-stage breast cancer. These risk prediction tools include different patient and tumour characteristics and may give different predictions for the same patient (see *Table 56, Appendix 1*).



**FIGURE 3** Diagnosis and management pathway in breast cancer. For postmenopausal women whose tumours are greater than grade 1, many centres also use adjuvant bisphosphonates for up to 3 years. Patients may also be treated with adjuvant radiotherapy depending on whether they have had a wide local excision or mastectomy and depending on the characteristics of the primary tumour; this may include radiotherapy to not only the breast but also the chest wall, supraclavicular fossa and lymph node and axillar. Neoadjuvant treatment may include Pertuzumab (Perjeta®, Roche Products Ltd) and trastuzumab. Adjuvant chemotherapy may be given alongside biological therapy. Reproduced with permission from Ward *et al.*<sup>1</sup> Contains information licensed under the Non-Commercial Government Licence v2.0. FISH, fluorescence in situ hybridisation.

The NICE CG80<sup>9</sup> does not make specific reference to the use of tumour profile tests to aid decision-making. However, the NICE Diagnostics Guidance (DG) 10 on tumour profiling<sup>20</sup> recommends onco<sup>type</sup> DX as an option for guiding adjuvant chemotherapy decisions for people with ER+, LNO, HER2- early-stage breast cancer at intermediate (clinical) risk if onco<sup>type</sup> DX is likely to help in the decision of whether or not to use adjuvant chemotherapy.

### Adjuvant! Online

The AOL computer program is designed to provide estimates of the benefits of adjuvant endocrine therapy and chemotherapy. The current version of AOL does not include *HER2* status and the potential benefit of trastuzumab. Patient and tumour characteristics are entered into the program and provide an estimate of the baseline risk of mortality or relapse for patients without adjuvant therapy. Information about the efficacy of different therapy options are derived from the EBCTCG meta-analyses in order to provide estimates of reduction in risk at 10 years of breast-cancer-related death or relapse for selected treatments. These estimates are then provided on printed sheets in simple graphical and text formats to be used in consultations. At the time of writing this report (October 2017), AOL was in the process of being updated and was not accessible.

### Nottingham Prognostic Index

The NPI is a composite prognostic parameter involving both time-dependent factors and aspects of biological aggressiveness. The NPI score is based on a combination of tumour grade, lymph node involvement and tumour size. To calculate the score, add numerical grade (1, 2 or 3), lymph node score (negative = 1, 1–3 nodes = 2, > 3 nodes = 3) and  $0.2 \times$  tumour size in cm. Patients can be divided into three prognostic groups on the basis of the NPI: a good prognosis group (NPI of  $\leq 3.4$ ), a moderate prognosis group ( $3.4 < \text{NPI} < 5.4$ ) and a poor prognosis group (NPI of  $> 5.4$ ).

### Predict (version 2.0)

Predict (version 2.0) is an online computer program designed to help women with breast cancer and their doctors make informed decisions about treatment with chemotherapy or endocrine therapy following breast cancer surgery. Predict version 2.0 was developed using data from > 5000 women with breast cancer from England and has been tested on data from another 23,000 women with breast cancer from around the world. Patient and tumour characteristics are entered into the program, which provides an estimate of the overall survival (OS) for patients with or without adjuvant hormone therapy, adjuvant chemotherapy and trastuzumab.

Clinical opinion suggests that there is variation in clinical practice between NHS trusts in the UK, with some centres using single risk prediction tools and others using multiple tools in combination, in addition to other clinical parameters.

## Description of technologies under assessment

Tumour profiling tests aim to improve the use of chemotherapy in breast cancer by improving the categorisation of patients in accordance with ROR or death, and by identifying those patients who will gain most benefit from chemotherapy. Tests predicting the ROR in a specific population are likely to be used after surgery, in conjunction with other information available about tumour size, grade, nodal status and other factors to guide the use of adjuvant chemotherapy. Tests that require samples to be sent away for central review, following surgery, may introduce a short delay (of up to 3 weeks) before the decision can be taken on whether or not to offer chemotherapy.

Five tests were identified in the final NICE scope<sup>21</sup> and are included in this assessment: four are based on gene expression profiling [EndoPredict® (Myriad Genetics Ltd, London, UK), onco<sup>type</sup> DX® (Genomic Health, Inc., Redwood City, CA, USA), MammaPrint® (Agendia, Inc., Amsterdam, the Netherlands) and Prosigna® (NanoString Technologies, Inc., Seattle, WA, USA)] and one is based on immunohistochemistry 4 (IHC4).

### Gene expression profiling tests

Gene expression profiling tests investigate the expression of specific panels of genes (also known as gene profiles or gene signatures). They do this by assessing the identity and number of messenger ribonucleic acid (mRNA) transcripts in a specific tissue sample. As only a fraction of the genes encoded in the genome of a cell are expressed by being transcribed into mRNA, gene expression profiling provides information about the activity of genes that give rise to these mRNA transcripts. Given that mRNA molecules are translated into proteins, changes in mRNA levels are ultimately related to changes in the protein composition of the cells, and consequently to changes in the properties and functions of tissues and cells (both normal and malignant) in the body. Gene expression profiling tests work by making use of different techniques to measure mRNA levels in breast cancer specimens including real-time reverse transcription-polymerase chain reaction (RT-PCR) and deoxyribonucleic acid (DNA) microarrays.

There are various ways of preparing the ribonucleic acid (RNA), and different protocols may be used to prepare the specimens [e.g. formalin-fixed, paraffin-embedded (FFPE), snap-frozen and fresh samples]. The tests included in this assessment use FFPE tissue and do not require the use of fresh samples. Furthermore, there are varying algorithms that can be used to combine the raw data to obtain a summary measure. All of these factors can affect the reproducibility and reliability of gene expression profiling tests. These tests provide an estimate of the ROR.

### Immunohistochemical-based tests

Immunohistochemistry (IHC) markers are being developed to provide similar information to that given by gene expression profiling tests. Some of these tests offer the advantage of using existing IHC technology (such as ER and HER2 markers) that is routinely available in all UK pathology departments, although methods for quantifying these markers in the format required for the test may not be routinely available.

### Summary of tumour profiling tests included in the assessment

The key features of the five tests are summarised in the following sections and in *Table 1*.

#### EndoPredict (Myriad Genetics)

EndoPredict is a Conformité Européenne (CE)-marked assay that is designed to assess the risk of distant recurrence within 10 years of initial diagnosis. The test is intended for use in premenopausal and postmenopausal women with early-stage breast cancer with all of the following clinical features:

- oestrogen receptor positive
- human epidermal growth factor receptor 2 negative (HER2-)
- lymph node negative (no positive nodes) or lymph node positive (LN+) (up to three positive nodes).

EndoPredict measures the expression of 12 genes: three proliferation-associated genes, five hormone receptor-associated genes, three reference (normalisation) genes and one control gene.

EndoPredict requires RNA samples extracted from FFPE breast cancer tissue. The test can be conducted in a local laboratory using a VERSANT® kPCR Amplification Detection Module (Siemens Healthcare Diagnostics Inc, Erlangen, Germany). Alternatively, FFPE samples can be submitted to a Myriad Genetics pathology laboratory in Munich that is accredited by the Deutsche Akkreditierungsstelle, a national accreditation body for Germany.

The test process involves using a reverse transcription-quantitative polymerase chain reaction (RT-qPCR), in which target mRNAs are reverse transcribed, amplified and simultaneously detected. The raw data are then exported to online evaluation software (EndoPredict Report Generator; Myriad Genetics Ltd, London, UK), which performs a quality check and calculates the EndoPredict score and the EndoPredict Clinical (EPclin) score. The EndoPredict score is a number on a scale from 0 to 15, is the molecular score only and is not the final test result. An EndoPredict score of < 5 indicates a low risk of distant disease recurrence in the next 10 years. An EndoPredict score of  $\geq 5$  indicates a high risk of distant disease recurrence in the

**TABLE 1** Summary of technologies included in the assessment

Features	Test				
	EndoPredict (Myriad Genetics)	MammaPrint (Agendia)	Oncotype DX (Genomic Health)	Prosigna (NanoString Technologies)	IHC4
Purpose	Recurrence risk	Recurrence risk and chemotherapy benefit	Recurrence risk and chemotherapy benefit	Recurrence risk and intrinsic subtype	Recurrence risk
Description	12-gene assay (eight cancer genes; RT-qPCR) plus clinical factors	70-gene array (microarray)	21-gene assay (16 cancer genes; RT-qPCR)	50-gene assay (50 cancer genes; direct mRNA counting) plus clinical factors	4 IHC tests (ER, PR, <i>HER2</i> , Ki-67). IHC4+C includes IHC4 plus clinical factors
Testing location	Local laboratory or test service (Germany)	Test service (the Netherlands)	Test service (USA)	Local laboratory or test service (UK)	Local laboratory
Stage	Early stage	Early stage (stage I or II)	Early stage (stage I or II)	Early stage (stage I to IIIA)	Early stage
Lymph node status	LN0 and LN+ (up to three positive)	LN0 or LN+ (up to three positive)	LN0 or LN+ (up to three positive)	LN0 and LN+	LN0 and LN+ (1 to three positive nodes)
Hormone receptor status	ER+	ER+ or ER-	ER+	ER+	ER+
<i>HER2</i> status	Negative	Negative or positive	Negative	Negative	Negative or positive
Menopausal status	Premenopausal and postmenopausal	Premenopausal and postmenopausal	Premenopausal and postmenopausal	Postmenopausal	Postmenopausal
Test result	Low risk or high risk	Low risk or high risk	Low risk, intermediate risk or high risk	Low risk, intermediate risk or high risk Intrinsic subtype	Low risk, intermediate risk or high risk
Assumptions	Score assumes 5 years of hormonal treatment	Assumes no therapy	Score assumes 5 years of hormonal treatment	Score assumes 5 years of hormonal treatment	Score assumes 5 years of hormonal treatment
Commercially available in England?	Yes	Yes	Yes	Yes	No
Cost	£1500	£2326 (based on conversion from Euros to pounds sterling)	£2580 (excludes PAS)	£1650 (kit cost only)	£202.52 (inflated to 2016 values)

ER-, oestrogen receptor negative; LN+, lymph node positive; PR, progesterone receptor.

next 10 years. The EPclin score is calculated by adding clinical data about tumour size and nodal status to the EndoPredict score. From the EPclin score, the probability of metastasis formation within 10 years is estimated, assuming 5 years of hormonal treatment. The EPclin score (cut-off point of 3.3) provides a single low-/high-risk cut-off point; the threshold was set such that women with a low-risk result (EPclin score of < 3.3) have a < 10% risk of developing distant metastases over the next 10 years. It takes approximately 2 days to obtain the test results if the test is done in-house. If samples are sent away for testing, the turnaround time for the central service is 4 to 5 working days.

### MammaPrint (Agendia)

MammaPrint is a CE-marked microarray that is designed to assess the risk of distant recurrence within 5 and 10 years and whether or not a woman would benefit from chemotherapy. The test is intended for use in premenopausal and postmenopausal women with stage I or II breast cancer with the following clinical features:

- tumour size of  $\leq 5$  cm
- lymph node negative or positive (up to three positive nodes).

The test can be used irrespective of ER and *HER2* status; that is, it can be used for tumours that are ER negative (ER-) or ER+ and *HER2*- or human epidermal growth factor receptor 2 positive (*HER2*+). MammaPrint measures the expression of 70 genes, including genes associated with seven different parts of the metastatic pathway: (1) growth and proliferation, (2) angiogenesis, (3) local invasion, (4) entering the circulation, (5) survival in the circulation, (6) entering organs from the circulation and (7) adaptation to the microenvironment at a secondary site. The MammaPrint test is offered as an off-site service. In Europe, samples are sent for analysis at the Agendia laboratory in Amsterdam, the Netherlands. The test requires a FFPE breast cancer tissue sample from a surgical specimen or core needle biopsy.

The test process involves isolation of RNA from a FFPE sample followed by reverse transcription of the mRNA to get complementary DNA (cDNA). The cDNA is amplified and labelled before being hybridised (bound) to the diagnostic microarray. The microarray is washed and then scanned using an Agilent Technologies, Inc. DNA microarray scanner (Santa Clara, CA, USA). The scan file is analysed using Agilent Technologies, Inc. Feature Extraction Software (Santa Clara, CA, USA) and an algorithm is used to calculate the correlation of the sample profile to a 'low risk' template profile on a scale of -1.000 to +1.000 with a cut-off point of 0. The threshold was set such that women with a low-risk result have a 10% risk of developing distant metastases over the next 10 years without any adjuvant hormone therapy or chemotherapy. Test results are available to health-care professionals within 10 days of submitting the sample.

### Oncotype DX Breast Recurrence Score (Genomic Health)

Oncotype DX is designed to assess the risk of distant recurrence within 10 years and predict the likelihood of benefit from chemotherapy. The test also reports the underlying tumour biology: ER, progesterone receptor (PR) and *HER2* status. The test is intended for use in premenopausal and postmenopausal women with stage I or II breast cancer that has the following clinical features:

- lymph node negative or positive (up to three positive nodes)
- oestrogen receptor positive
- human epidermal growth factor receptor 2 negative.

Oncotype DX quantifies the expression of 21 genes. Of these, 16 are cancer-related genes correlated with distant recurrence/relapse-free survival (DRFS) and five are reference genes for normalising the expression of the cancer-related genes. This information is used to calculate the Breast Recurrence Score.

Oncotype DX is offered as a test service to the NHS. Samples are processed centrally at the Genomic Health laboratory in the USA, which is accredited by the American Association for Laboratory Accreditation and the College of American Pathologists. The test requires a FFPE breast cancer tissue sample from a

biopsy or surgical resection, which can be sent as a paraffin-embedded block or as 15 unstained charged slides. The test process is based on RT-qPCR. The test gives a recurrence score of between 0 and 100, which is used to quantify the 10-year risk of distant recurrence, assuming 5 years of hormonal (endocrine) therapy. Based on current cut-off points for the *oncotype* DX test, a score of < 18 indicates low risk of distant recurrence, a score between 18 and 30 indicates intermediate risk and a score of  $\geq 31$  indicates high-risk. It should be noted that a number of studies, including the ongoing Trial Assigning Individualized Options for Treatment (Rx) (TAILORx) study,<sup>22</sup> are testing the use of different cut-off points for *oncotype* DX. The recurrence score may also predict the benefit of chemotherapy. The *oncotype* DX results are typically reported within 7–10 days after the sample is received at the laboratory.

The *oncotype* DX Breast Recurrence Score can be combined with clinical and pathological factors (tumour size, tumour grade and patient age) using the recurrence score–pathology–clinical (RSPC) calculator; however, this calculator has not been validated.

### Prosigna (NanoString Technologies)

Prosigna is a CE-marked assay designed to assess DRFS at 10 years. The test is intended for use in postmenopausal women with early-stage breast cancer that is:

- lymph node negative or positive (up to three positive nodes)
- oestrogen receptor positive
- human epidermal growth factor receptor 2 negative.

The test requires RNA extracted from a FFPE breast tumour tissue sample and is done using the nCounter® analysis system (NanoString Technologies, Inc., Seattle, WA, USA). The test process involves fluorescent probe pairs that hybridise to the mRNA; the fluorescence is then detected by the nCounter Digital Analyzer (NanoString Technologies, Inc., Seattle, WA, USA).

Prosigna is based on the Prediction Analysis of Microarray 50 (PAM50) gene signature.<sup>23</sup> It measures the expression levels of 50 genes used to classify patients into one of four breast cancer subtypes. It also measures the expression of eight housekeeping genes used for signal normalisation, six positive controls and eight negative controls. Prosigna classifies samples into the following breast cancer subtypes based on their PAM50 gene expression signatures: luminal A, luminal B, *HER2*-enriched or basal-like. A ROR score, representing the risk of distant recurrence within 10 years (assuming 5 years of hormonal treatment), is then derived from an algorithm based on the results of the PAM50 gene signature plus clinicopathological factors. Four versions of the ROR score exist in the research setting: (1) ROR based on PAM50 subtype information (ROR-S), (2) ROR-S based on PAM50 information plus proliferation score (ROR-P), (3) ROR-S plus tumour size (ROR-T or ROR-C) and (4) ROR-S plus proliferation score and tumour size [PAM50 subtype call, proliferation score and ROR score (ROR-PT)]. The proliferation score is based on a subset of the PAM50 genes associated with the proliferation pathway.

The Prosigna test uses ROR-PT and therefore includes the PAM50 breast cancer subtype, tumour size and proliferation score. Nodal status is also used in converting the score into a risk category. The ROR score is a numerical score on a scale of 0 to 100. Based on this score and the nodal status, samples are classified into risk categories:

- node negative: low risk (score of 0–40), intermediate risk (score of 41–60) or high risk (score of 61–100)
- node positive (up to three positive nodes): low risk (score of 0–15), intermediate risk (score of 16–40) or high risk (score of 41–100).

This assessment includes all studies assessing ROR-PT, whether they use the commercial Prosigna test (using the nCounter system) or other methods (such as RT-qPCR). However, studies assessing ROR-S (subtype), ROR-T/ROR-C (subtype and tumour size) or ROR-P (subtype and proliferation score) are excluded. Studies are also excluded if they only assess PAM50 breast cancer subtypes (luminal A, etc.) rather than ROR-PT score.

## IHC4 test

Immunohistochemistry 4 is a laboratory-developed test that combines the results of four IHC-measured parameters. The test can be combined with clinical and pathological features; this is known as IHC4 plus clinical factors (IHC4+C). The test is designed to quantify the risk of distant recurrence in breast cancer patients, assuming 5 years of endocrine therapy. The test is intended for use in postmenopausal women with early-stage breast cancer with the following clinical features:

- oestrogen receptor positive
- lymph node negative or positive (up to three positive nodes).

The components of the test are four immunohistochemical assays: ER, PR, *HER2* and the proliferation marker Ki-67. The IHC4 test is currently used within the Royal Marsden Breast Cancer Unit service, but it has been suggested that the test could be run in local NHS laboratories if quality assurance programmes for the individual assays were in place. IHC4 uses FFPE breast tumour tissue samples and IHC techniques that are universally available in NHS pathology departments. ER and *HER2* markers are commonly measured in NHS laboratories, although methods for quantifying these markers in the format required for the test may not be routinely available. Although PR and Ki-67 markers are not routinely measured in breast tumour tissue samples, the assays are commonly available for use if needed. The quantitative assessment of Ki-67 required for the IHC4 test is not currently conducted in most NHS laboratories and, therefore, further training for pathologists and biomedical scientists is likely to be needed.

The IHC4+C test involves an algorithm that calculates a risk score for distant recurrence based on the results of the four IHC assays and clinical factors including age, nodal status, tumour size and tumour grade. The algorithm has been published and validated<sup>24,25</sup> and is freely available, and a calculator is available for use on request. A distant recurrence score of < 10% is categorised as low risk for distant recurrence at 10 years, a score of  $\geq 10\%$  but < 20% is categorised as intermediate risk and a score of  $\geq 20\%$  is categorised as high risk for distant recurrence at 10 years. At the Royal Marsden NHS Foundation Trust, the test is processed with an average estimated turnaround time of 1 week; however, results may be made available in 2 working days if they are urgently required.

### Current usage of tumour profiling tests in the NHS

A previous systematic review and economic evaluation (Ward *et al.*<sup>1</sup>) published in 2013 considered the clinical effectiveness and cost-effectiveness of tumour profiling tests compared with current prognostic tools in guiding the use of adjuvant chemotherapy in people with early-stage breast cancer in England and Wales. This report informed the NICE decision to approve the use of *oncotype DX* as an option for guiding adjuvant chemotherapy decisions for people with ER+, LNO, *HER2*- early-stage breast cancer assessed to be at intermediate ROR of breast cancer after surgery. The use of the other tumour profiling tests in the NHS remains limited (mainly to clinical trial use).

## Description of the decision problem

This assessment aims to assess whether or not tumour profiling tests used for guiding adjuvant chemotherapy decisions for people with early-stage breast cancer represent a clinically effective and cost-effective use of NHS resources.

### Interventions

The following tumour profiling tests are included, in combination with current decision-making:

- EndoPredict and EPclin
- MammaPrint
- *oncotype DX* Breast Recurrence Score and *oncotype DX* breast RSPC
- Prosigna (or ROR-PT, which is equivalent)
- IHC4 and IHC4+C.

### Comparators

The comparator for the assessment is standard UK practice for chemotherapy decision-making, which may include any tool, or clinical and pathological features, used to assess risk. Clinicopathological tools used in current practice include Predict, NPI and AOL. The use of these tools varies between centres.

### Population and important subgroups

The intended population for the assessment relates to people with ER+ (and/or PR-positive), HER2–, early-stage breast cancer (stages I or II) with zero to three positive lymph nodes (LN0–3).

In practice, it was anticipated that many potentially relevant studies would include a broader population. Therefore, all relevant studies of early-stage breast cancer were eligible for inclusion, and the findings are interpreted with reference to how closely the study population matched the intended population.

The following subgroups are considered within this assessment:

- people with LN0 cancer, people with micrometastases in the lymph nodes and people with one to three positive lymph nodes (LN1–3)
- premenopausal and postmenopausal women
- people predicted to be at low, intermediate or high risk using a risk assessment tool or using clinical and pathological features
- males and females
- people of different ethnicities.

These tests will only have an impact on the health of patients if they lead to changes in patient management. This is most likely to happen in populations in which the decision of whether or not to offer chemotherapy is currently uncertain. One such group is patients with ER+, LN0, HER2– early-stage breast cancer for whom prognostic variables suggest that they are at intermediate risk. The definition of this 'intermediate group' is not clear cut. Clinical advice suggests that patients with a NPI of  $\leq 3.4$  are typically considered at low risk either using current prognostic tools (except for a few very young women with aggressive early-stage breast cancer) or based on the new tests and are unlikely to receive chemotherapy; therefore, their management is unlikely to change. Few patients with ER+, LN0, HER2– early-stage breast cancer will have a NPI of  $> 5.4$  and, therefore, those with a NPI of  $> 3.4$  can be considered as being at intermediate risk. Some LN+ patients may also be considered to be at intermediate risk.

Current treatment protocols indicate that women with HER2+, ER– early-stage breast cancer or with more than three positive nodes are likely to receive chemotherapy in most centres in England. Although the use of tumour profiling tests might be able to spare a proportion of these patients from chemotherapy, the evidence base for the use of these tests in this population is more limited and clinical opinion, therefore, considered the assessment of these tests in this population to be a lower priority; this population was therefore excluded from the NICE scope. Currently, patients with micrometastases who are clinically managed as LN0 patients are excluded from NHS-funded testing using *oncotype DX*, even if they fall within the intermediate-risk group. Patients with micrometastases are included in the NICE scope.

Patients with ER+, HER2– early-stage breast cancer, who either are LN0 or have one to three positive nodes, are therefore considered to be an important population in which to assess these tests, given the current evidence base. The scope therefore focuses on the ER+, HER2– population with zero to three lymph nodes. Within this population, an important subgroup consists of patients at clinically intermediate risk for whom the decision about whether or not to offer chemotherapy is not clear cut.

## Outcomes

The clinical effectiveness review considers the clinical effectiveness of the tests in relation to the following broad categories (these are described further in *Chapter 2, Methods*, which also lists the relevant study designs for each outcome):

- Analytic validity (i.e. the ability of the test to accurately and reliably measure the expression of mRNA or proteins by breast cancer tumour cells). Owing to time constraints, it was not possible to conduct a full review of analytic validity for all tests. A rapid review of IHC4 was conducted.
- Prognostic ability (i.e. the degree to which the test could accurately predict the risk of an outcome such as disease recurrence and discriminate patients with different outcomes).
- Prediction of chemotherapy benefit (i.e. whether or not the effect of chemotherapy vs. no chemotherapy on patient outcomes differs between test risk groups).
- Clinical utility (this is defined differently throughout the prognostic literature); here, we define clinical utility studies as those that assess the ability of the test to affect patient outcomes (e.g. recurrence and survival) through the prospective use of the test to guide treatment decisions.
- Decision impact (i.e. how the tests influence decision-making in terms of which patients will be offered or administered chemotherapy; this design does not include follow-up of clinical outcomes such as recurrence or survival). The review included only UK and European studies because chemotherapy rates differ widely between European and non-European countries.
- Health-related quality of life and anxiety.
- Time-to-test results.

Assessment of the above outcomes involves making comparisons (between study groups or between risk groups for the test) in terms of clinical patient outcomes such as recurrence and survival. Key clinical outcomes included for this purpose are listed in *Chapter 2, Methods*.

The outcomes of interest for the economic evaluation are the morbidity and mortality associated with invasive breast cancer and its treatment. Outcomes from the model are expressed in terms of the incremental cost per quality-adjusted life-year (QALY) gained.

## Aims and objectives of the assessment

The overall aim of the assessment is to address the question ‘Do tumour profiling tests used for guiding adjuvant chemotherapy decision in patients with early-stage breast cancer represent a clinically effective and cost-effective use of NHS resources?’. This includes an update of the systematic review and cost-effectiveness analysis<sup>1</sup> undertaken to inform NICE DG10.<sup>20</sup>

The objectives of the assessment are to:

- conduct a systematic review of the published evidence on the effectiveness and cost-effectiveness of the five tumour profiling tests
- develop a health economic model to assess the cost-effectiveness associated with the use of tumour profiling tests compared with current prognostic tools to guide the use of adjuvant chemotherapy in early-stage breast cancer from the perspective of the NHS and Personal Social Services (PSS).



## Chapter 2 Clinical evidence

A systematic review was undertaken to assess the effectiveness of tumour profiling tests for guiding adjuvant chemotherapy decisions in early-stage breast cancer. The methods of the systematic review are described in *Methods*. The results of the review are reported in *Results*.

### Methods

This report contains reference to confidential information provided as part of the NICE appraisal process. This information has been removed from the report and the results, discussions and conclusions of the report do not include the confidential information. These sections are clearly marked in the report.

A registered protocol of this systematic review (CRD42017059561) is available on the PROSPERO website at [www.crd.york.ac.uk/prospero/display\\_record.asp?ID=CRD42017059561](http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42017059561) (accessed 10 May 2018). The review was conducted following the general principles recommended in the Centre for Reviews and Dissemination (CRD)'s guidance,<sup>26</sup> in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement,<sup>27</sup> in the NICE Diagnostic Assessment Programme manual<sup>28</sup> and by the Cochrane Prognosis Methods Group.<sup>29</sup>

The protocol included a mapping stage, following which minor amendments were made to the inclusion criteria and review methods in consultation with NICE and clinical advisors in order to focus the evidence review to studies of most relevance to the decision problem.

### Identification of studies

This systematic review search provided an update to the previous systematic review (by Ward *et al.*<sup>1</sup>) conducted for NICE DG10.<sup>20</sup> The search strategy was adapted to retrieve clinical studies and systematic reviews of five tumour profiling tests (with or without clinicopathological factors) in early-stage breast cancer management: EndoPredict, oncotype DX, MammaPrint, IHC4 and Prosigna.

The search approach involved:

- searching of electronic databases
- contact with experts in the field
- scrutiny of bibliographies of retrieved papers
- identification of relevant studies from the previous review by Ward *et al.*<sup>1</sup> conducted for NICE DG10<sup>20</sup> (see below)
- references included within the evidence dossiers provided by the manufacturers to NICE.

### Electronic database searches

The search strategy comprised medical subject headings (MeSHs) or Emtree thesaurus terms and free-text synonyms for 'breast cancer' combined with the individually named tumour profiling tests. Searches were translated across databases and were not limited by language. Searches for oncotype DX, MammaPrint, IHC and Prosigna were limited by publication date from 2011 (the search date in the review by Ward *et al.*<sup>1</sup> because these tests were included in this review), whereas no date limits were applied to EndoPredict (as it was not included in the review by Ward *et al.*<sup>1</sup>).

The search strategies are presented in *Appendix 2*. Literature searching was undertaken in February 2017 in the following electronic databases and trials registries:

- MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations (via Ovid): 1946 to present.
- EMBASE (via Ovid): 1974 to 24 February 2017.

- Cochrane Database of Systematic Reviews (via Wiley Interscience): 1996 to present.
- Database of Abstracts of Reviews of Effects (via Wiley Interscience): 1995 to 2015 (until close of database).
- Cochrane Central Register of Controlled Trials (via Wiley Interscience): 1995 to present.
- Health Technology Assessment (HTA) Database (via Wiley Interscience): 1995 to 2016 (until close of database).
- NHS Economic Evaluation Database (via Wiley Interscience): 1995 to 2015 (until close of database).
- Science Citation Index Expanded (via Web of Science): 1900 to present.
- Conference Proceedings Citation Index – Science (via Web of Science): 1990 to present.
- World Health Organization International Clinical Trials Registry Platform (<http://apps.who.int/trialsearch/>; accessed 19 January 2017) (no date limit applied).
- American Society of Clinical Oncology (ASCO) (via Web of Science) (date range searched: 2011–17).
- European Society for Medical Oncology (via Web of Science) (date range searched: 2011–17).

### Supplementary searches

References of relevant systematic reviews, primary studies and company submissions were checked to identify additional studies.

### Inclusion and exclusion criteria

The inclusion and exclusion criteria for selecting studies are described in the following sections.

### Population and setting

The intended population included people with ER+ (and/or PR-positive), HER2–, early-stage breast cancer (stages I or II) with LN0–3.

In practice, it was anticipated that many potentially relevant studies would include a broader population. Therefore, all relevant studies of early-stage breast cancer were eligible for inclusion. When subgroups were reported for the intended population (described above), these were used in the assessment. When no subgroups were reported, the study was included and the findings were interpreted with reference to how closely the study population matched the intended population.

The following subgroups were considered within this assessment:

- people with LN0 cancer, people with micrometastases in the lymph nodes and people with LN1–3
- premenopausal and postmenopausal women
- people predicted to be at low, intermediate or high risk using a risk assessment tool or using clinical and pathological features
- males and females
- people of different ethnicities.

This assessment focuses on the use of tumour profiling tests to guide decisions about adjuvant chemotherapy. The use of these tests to guide endocrine therapy decisions, or decisions about neoadjuvant chemotherapy (to shrink the tumour before surgery), was not evaluated.

### Interventions

The following tumour profiling tests were included:

- EndoPredict and EPclin
- MammaPrint
- oncotype DX Breast Recurrence Score and oncotype DX Breast RSPC
- Prosigna (or ROR-PT, which is equivalent)
- IHC4 and IHC4+C.

### Commercial versus in silico tests

Studies were included if they assessed the commercially available versions of the tests. For IHC4, as there is no commercially available version of the test, any methodology was included. In addition, some studies used in silico (electronic database) versions of tests using publicly available genetic databases, usually based on whole-genome-expression microarray data. Owing to uncertainty about their similarity to the commercially available tests, these studies were analysed separately. It was beyond the scope of the review to ascertain the quality of the methods used or the degree of overlap between cohorts for these in silico studies.

### Comparators

The comparator for the assessment is standard UK practice for chemotherapy decision-making. This was taken to include combinations of clinicopathological factors (e.g. within multivariable models), plus clinicopathological risk tools used in the UK, including Predict, the NPI and AOL. The clinical treatment score (CTS), a combination of commonly used clinicopathological variables, was also included as a comparator even though it is not commonly used in practice as a tool, because it is used in a number of key studies and includes a set of variables that are used in practice.

Other non-UK local or national guidelines, such as St Gallen and the National Comprehensive Cancer Network (NCCN) guidelines, were excluded when a study also reported comparisons with Predict, NPI or AOL, but were otherwise included.

Relevant comparators within individual studies varied in accordance with the study type:

- Studies assessing prognostic performance. No comparator is needed as the aim is to compare outcomes between risks groups for the test being studied.
- Studies assessing prediction of chemotherapy benefit. No comparator is needed as the aim is to compare the effect of chemotherapy between risks groups for the test being studied.
- Clinical utility studies. The relevant comparator is standard clinical practice as defined in the first paragraph of this section.
- Decision impact studies. The relevant comparator is standard clinical practice as above (for pre-test chemotherapy decisions).

### Outcomes and study designs

The clinical effectiveness review considers the clinical effectiveness of the tests in relation to the following broad categories:

- Analytic validity (i.e. the ability of the test to accurately and reliably measure the expression of mRNA or proteins by breast cancer tumour cells). Owing to time constraints, it was not possible to conduct a full review of analytic validity for all tests. A rapid review of IHC4 was conducted.
- Prognostic performance (i.e. the degree to which the test can accurately predict the risk of an outcome such as disease recurrence and discriminate patients with different outcomes). This is usually assessed by conducting the test on stored tumour samples for which longer-term patient outcome data are available, but when the test did not influence treatment. Study designs include –
  - Reanalysis of randomised controlled trial (RCT) data.
  - Analysis of prospective or retrospective cohorts in which the test did not influence treatment.
- Prediction of chemotherapy benefit (i.e. whether or not the effect of chemotherapy vs. no chemotherapy on patient outcomes differs between test risk groups). This is usually assessed by conducting the test on stored tumour samples for which longer-term outcome data are available. Study designs include –
  - Reanalysis of RCTs in which some patients received chemotherapy and some did not.
  - Analysis of prospective or retrospective cohorts in which some patients received chemotherapy and some did not. These could include cohorts in which the test did or did not influence practice.

- The difference between absolute and relative benefit should be noted: for a test that is prognostic, a difference in absolute benefit of chemotherapy between groups would be expected, whereas for a test to be considered predictive of chemotherapy benefit, a difference in relative benefit should be seen. As an example, if distant recurrence rates in the test high-risk group were 30% without chemotherapy and 20% with chemotherapy, the absolute benefit of chemotherapy would be 10%. Likewise, if distant recurrence rates in the test low-risk group were 3% without chemotherapy and 2% with chemotherapy, the absolute benefit of chemotherapy would be 1% (i.e. much smaller). However, the relative benefit would be the same in both groups [relative risk (RR) of 0.67, i.e. chemotherapy reduces recurrence by one-third]. If the test is predictive of chemotherapy benefit, the RR would be expected to be different in different risk groups.
- Clinical utility: this is defined differently throughout the prognostic literature. Here, we define clinical utility studies as those that assess the ability of the test to affect patient outcomes (such as recurrence and survival) through the prospective use of the test to guide treatment decisions (the study may be prospective or retrospective, but use of the test should have been prospective, i.e. used in clinical practice rather than conducted on stored tumour samples). Study designs include –
  - RCTs randomising patients to chemotherapy guided by the test or guided by a comparator (e.g. clinical practice).
  - Observational studies reporting clinical outcomes for patients whose treatment was guided by the test. As these studies do not have a comparator, we are primarily interested in outcomes for patients with low-risk disease, who, as a group, have mostly avoided chemotherapy. The observation of good outcomes in this group could, alongside other evidence, support the avoidance of chemotherapy in this group.
- Decision impact (i.e. how the tests influence decision-making in terms of which patients will be offered chemotherapy). Clinical advice to the External Assessment Group (EAG) suggests that chemotherapy rates differ between countries, with lower rates in the UK and Europe than in the USA. The review therefore included only UK and European studies. Study designs include –
  - Studies assessing change in chemotherapy recommendations and/or decisions before and after use of the test (this design does not include follow-up of clinical outcomes such as recurrence or survival).
- Health-related quality of life and anxiety. Study designs include –
  - Studies assessing impact of the test versus usual practice on HRQoL and anxiety.
  - Studies assessing HRQoL and anxiety before and after test use.
- Time-to-test results: studies assessing the time taken to obtain test results.
- Concordance: concordance is defined in this review as the degree to which tests assign the same patients to the same risk groups. Such studies do not report long-term outcomes. A full systematic review of studies that only assess concordance between tests (with no patient outcome data) was beyond the scope of this assessment. However, the Optimal Personalised Treatment of early breast cancer using Multi-parameter Analysis preliminary (OPTIMA Prelim) study<sup>30</sup> was included as a key example of concordance between tests.

### ***Clinical patient outcomes***

Assessment of clinical utility, prognostic ability and prediction of chemotherapy benefit involves making comparisons (between study groups or between risk groups for the test) in terms of clinical patient outcomes. Key clinical outcomes included for this purpose are listed below. Standard definitions for breast cancer outcomes, defined by Hudis *et al.*,<sup>31</sup> are given below, although these are not always consistently or clearly defined in study reports. Within this review, DRFS and distant recurrence/relapse-free interval (DRFI)

have been combined in some sections where insufficient detail was provided in study reports to distinguish between them. The standard definitions for breast cancer outcomes are:

- distant recurrence/relapse-free survival, also referred to as distant metastasis-free survival (DMFS) or distant disease-free survival (DFS) – events include distant recurrence and death from any cause
- distant recurrence/relapse-free interval, also referred to as distant metastasis-free interval (DMFI) – events include distant recurrence and death from breast cancer
- recurrence/relapse-free survival (RFS) – events include ipsilateral, locoregional or distant invasive recurrence and death from any cause [not contralateral disease, non-breast cancers or ductal carcinoma in situ (DCIS)]
- recurrence/relapse-free interval (RFI) – events include ipsilateral, locoregional or distant recurrence and death from breast cancer (not contralateral disease, non-breast cancers or DCIS)
- invasive disease-free survival (IDFS) – events include ipsilateral, locoregional or distant invasive recurrence, contralateral and non-breast cancers, and death from any cause (not DCIS)
- disease-free survival – events include ipsilateral, locoregional or distant recurrence, DCIS, contralateral or non-breast cancers, and death from any cause
- breast-cancer-specific survival (BCSS) – events include breast cancer death only
- overall survival – events include death from any cause only
- disease-related morbidity and mortality
- chemotherapy-related morbidity and mortality.

For the above clinical outcomes, studies were only included if follow-up was  $\geq 5$  years for survival outcomes (OS and BCSS) or  $\geq 3$  years for other outcomes.

The following outcomes were excluded:

- locoregional recurrence (i.e. within the region of the original tumour), because chemotherapy decisions will mainly impact distant recurrence and survival
- clinician confidence and patient decisional conflict relating to decision impact of the test (this is beyond the scope of this assessment)
- prediction of benefit from one type of chemotherapy versus another (the assessment is restricted to benefit of chemotherapy vs. no chemotherapy).

Studies not published in the English language were included if sufficient PICOS (population, intervention, comparator, outcome, study design) data could be extracted from non-English-language full-texts or from an existing English language abstract. Non-peer-reviewed reports or abstracts were only included if the data were presented in a succinct and accessible manner (e.g. a manuscript prepared for submission to a journal), if sufficient methodological details were reported to allow critical appraisal of the study quality and if results were reported in sufficient detail.

### Study selection process

All records retrieved from the search were exported into a reference management database [EndNote version X7; Clarivate Analytics (formerly Thomson Reuters), Philadelphia, PA, USA]. After deduplication, titles/abstracts were assessed for relevance, followed by examination of full texts of potentially includable studies. Study selection was conducted by one reviewer, with discussion between two reviewers for any studies giving rise to uncertainty. A 10% sample was checked by a second reviewer early in the process to ensure mutual understanding of study inclusion and to correct if necessary.

### Data extraction

A data extraction form was constructed in Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA) and piloted using two examples of each study design. Data were extracted by one reviewer and checked by a second reviewer. Disagreements were resolved by discussion. Study authors were contacted for any missing or ambiguous data when time allowed. When multiple publications related to the same patient cohort, or when pooled analyses were identified, the references selected for inclusion were those that

provided the most complete follow-up and the most useful clinical outcomes (DRFS or DRFI were preferred based on clinical advice and use in the health economic model; see *Chapter 3*), avoiding double-counting of patients/cohorts when possible.

### Quality assessment

The methodological quality of included studies was assessed using quality assessment tools relevant to the study design. Quality assessment was undertaken by one reviewer and checked by a second reviewer. The quality and design of studies was considered within the narrative synthesis of results.

For clinical utility studies (for which the highest level of evidence is a RCT of the test vs. usual practice), quality was assessed using the Cochrane risk-of-bias tool for RCTs.<sup>32</sup>

For studies assessing prognostic ability and prediction of chemotherapy benefit, quality was assessed using relevant criteria selected from the draft Prediction model study Risk Of Bias ASsessment Tool (PROBAST) (Dr Robert Wolff, Kleijnen Systematic Reviews Ltd, January 2017, personal communication). The PROBAST tool has been developed specifically for use in systematic reviews of prediction models by the Cochrane Prognosis Methods Group,<sup>29</sup> but is not yet validated or published. Criteria were selected on the basis of relevance to this review. *Table 2* shows the quality criteria used in this assessment and how they were scored.

Studies assessing decision impact, analytic validity and HRQoL/anxiety were not quality assessed owing to time constraints.

**TABLE 2** The PROBAST quality criteria and scoring

Number	Criterion	Scoring
<b>Risk-of-bias questions</b>		
1	Is the study design appropriate?	Yes (prognosis): reanalysis of RCT or cohort or nested case control AND patients did not receive chemotherapy Yes (predicting chemotherapy benefit): RCT or reanalysis of RCT No (prognostic): non-nested case control or case series AND/OR some/all patients had chemotherapy No (predicting chemotherapy benefit): patients not randomised to chemotherapy vs. no chemotherapy
2	Are all eligible patients included?	Yes: all eligible patients from trial or consecutive eligible patients from prospective registry No: some eligible patients excluded (e.g. not sent for testing, insufficient tissue, test failures, missing data, AND/OR non-prospective registry) Unclear: if unclear
4	Were test assessors blinded to clinical outcomes?	Yes: blinded No: not blinded Unclear: if unclear
6	Was the outcome definition standardised or defined a priori?	Yes: reported outcomes that were standardised (e.g. DRFS, OS) or defined a priori No: outcomes non-standardised and not defined a priori Unclear: if either item unclear

TABLE 2 The PROBAST quality criteria and scoring (continued)

Number	Criterion	Scoring
<b>Applicability questions</b>		
3	Does the patient spectrum match the review question?	Yes: all patients in scope (HR+, HER2-, LNO-3) Mostly: < 20% out of scope No: > 20% out of scope Unclear: if unclear
5	Is the test as per the decision problem?	Yes: same as commercially available tests or IHC4 conducted as per Cuzick <i>et al.</i> <sup>25</sup> No: different from commercially available tests (e.g. FFPE vs. fresh samples, test methods)

### Data presentation and synthesis

Data were summarised and presented as tabular and narrative syntheses. Meta-analysis was not considered appropriate owing to significant heterogeneity between studies. Interpretation of the evidence base was conducted with reference to published hierarchies for predictive studies<sup>33–35</sup> and with regard to the ability of the study design to adequately address the decision problem. Interpretation of results also considered how closely the study population matched the intended population, the methodological quality of the studies and the treatment received by patients (in terms of endocrine therapy and chemotherapy).

## Results

### Quantity of evidence

Figure 4 is the PRISMA flow diagram for study selection. The database searches and searches of other sources identified a total of 2330 unique references to screen. Of these, 1797 were excluded at the title/abstract stage and 533 full-text articles were screened, of which 380 were excluded (reasons are listed in Appendix 3). In total, 153 references were included in the assessment.

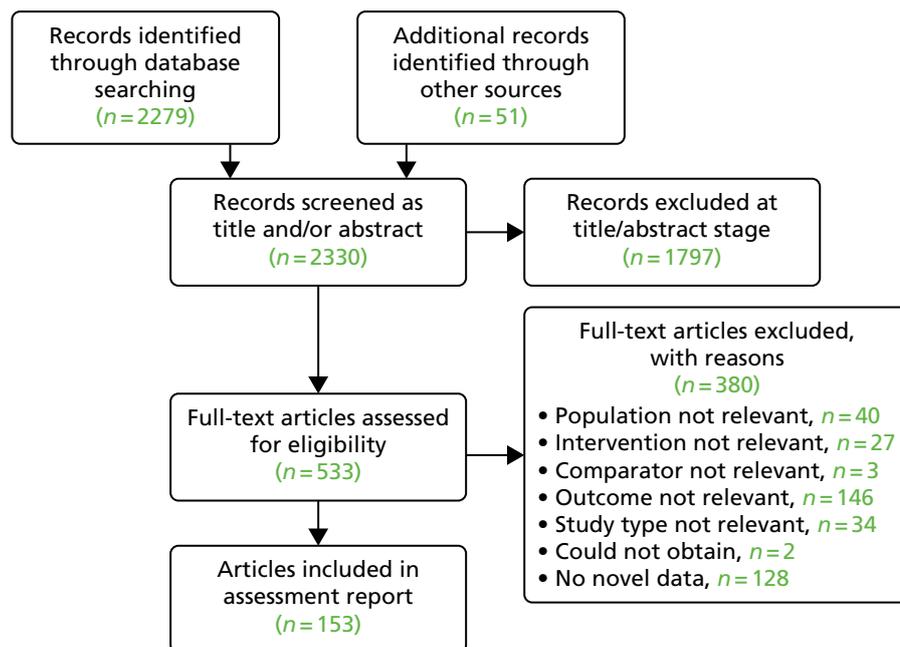


FIGURE 4 The PRISMA flow diagram.

There are numerous Translational substudies of the Arimidex, Tamoxifen, Alone or in Combination (TransATAC) publications that met the criteria for the review.<sup>25,36–44</sup> ATAC<sup>45</sup> was an international trial, which evaluated anastrozole alone, tamoxifen alone, and the combination of both treatments in breast cancer patients. Recruitment ended in 2006. TransATAC was a series of translational studies utilising samples and data from the ATAC trial. Throughout the report we present data provided by the TransATAC team as personal communications (Ivana Sestak, Queen Mary University of London, July 2017, personal communication) to the EAG, provided on request from the EAG, which restricts to UK patients in the tamoxifen arm, with hormone receptor-positive (HR+), HER2– and LNO–3 patients.<sup>46</sup> Subsequently, a very similar analysis was published by the TransATAC team.<sup>47</sup> Some concerns were expressed during the NICE consultation about the suitability of the TransATAC bespoke analysis and its comparability with other sources of data, and these are addressed in *Report Supplementary Material 1*.

### Overview of results

To orientate the reader to the broad sweep of the evidence and to facilitate interpretation of the detailed evidence base, a summary of the results is provided in *Appendix 4*. A more complete summary of DRFS/DRFI/DFS data for each test is then provided in section *Results: oncotype DX* through to *Time-to-test results*, with more detailed narrative syntheses (including outcomes OS and BCSS) in *Report Supplementary Material 2–10*. We have separated the evidence into the following broad categories:

- Development – a description of the development of the test. A full review of analytic validity was not possible owing to time constraints. A rapid review of IHC4 was conducted.
- Prognostic performance – studies reporting on the ability of the test to predict ROR and/or survival. The most commonly reported data are Kaplan–Meier estimates of risk of outcome per test risk group and hazard ratios (HRs) between groups, although a small number of studies report C-index data [which, in this case, are identical to the area under the curve (AUC)] and likelihood ratios. In keeping with the majority of studies, we first present unadjusted data, and separately report analyses (usually multivariable Cox proportional hazards models) that adjust for clinicopathological factors, which show whether or not the test potentially has prognostic value over clinicopathological variables. The C-index is a measure of the goodness of fit of a model with binary outcomes (in this case, it is identical to the AUC). A value of < 0.5 indicates a poor model, a value of 0.5 indicates that the model is no better than chance, a value of > 0.7 indicates a good model, a value of > 0.8 indicates a strong model and a value of 1 indicates a perfect model.<sup>48</sup>
- Chemotherapy benefit – studies in this category compare treatment benefit across risk categories, and most commonly reanalyse RCT data in which patients were randomised to chemotherapy or no chemotherapy, and conduct a test for the interaction between treatment and tumour profiling test risk group. The interaction test tells us whether or not the tumour profiling test is able to predict a differential treatment effect by risk group. We have also included any observational studies that report treatment benefit across risk categories, with or without interaction tests, with appropriate caveats about the possibility of confounding in such studies. Note that the difference between absolute benefit and relative benefit, as described in *Data extraction*, is of critical importance.
- Clinical utility – studies reporting the impact on patient outcomes (such as recurrence and survival) of the prospective use of the test to guide adjuvant chemotherapy treatment decisions. Ideally, such studies would randomise patients to treatment guided by the test or to treatment guided by usual clinical practice; however, given the paucity of RCT evidence, the inherent ethical issues with randomising all patients to chemotherapy and issues with powering such studies, observational studies have also been included in this section.
- Decision impact – studies that report the impact of test results on actual chemotherapy decisions or recommendations. Such studies do not report long-term follow-up of patients.

There were no data available for clinical utility for Prosigna, EndoPredict or IHC4. Chemotherapy benefit only applies to MammaPrint and oncotype DX, as only these tests claim to be able to identify patients who will benefit from chemotherapy, rather than just those patients who are at high risk of relapse. For this

reason, the clinical review comprises the following main sections in *Chapter 2*, each with a number of relevant subheadings:

- *Overview of results.*
- *Results: oncotype DX* (additional data in *Report Supplementary Material 2–4*).
  - *Development: oncotype DX.*
  - *Prognostic performance: oncotype DX.*
  - *Chemotherapy benefit: oncotype DX.*
  - *Clinical utility: oncotype DX.*
- *Results: MammaPrint* (additional data in *Report Supplementary Material 5*).
  - *Development: MammaPrint.*
  - *Prognostic performance: MammaPrint.*
  - *Chemotherapy benefit: MammaPrint.*
  - *Clinical utility: MammaPrint.*
- *Results: Prosigna* (additional data in *Report Supplementary Material 6*).
  - *Prognostic performance: Prosigna.*
- *Results: EndoPredict and EndoPredict Clinical* (additional data in *Report Supplementary Material 7*).
  - *Development: EndoPredict and EndoPredict Clinical.*
  - *Prognostic performance: EndoPredict and EndoPredict Clinical.*
- *Results: IHC4* (additional data in *Report Supplementary Material 8*).
  - *Development and analytic validity: IHC4.*
  - *Prognostic performance: IHC4 and IHC4+C.*
- *Results: decision impact studies* (additional data in *Report Supplementary Material 9*).
- *Anxiety and health-related quality of life.*
- *Time-to-test results.*

Additional sections that appear in *Report Supplementary Material* are:

- *Report Supplementary Material 1:* Comparison of TransATAC data to other study data (risk classification and prognosis).
- *Report Supplementary Material 8:* Narrative synthesis and additional tables for IHC4 analytical validity.
- *Appendix 5: results: all tests compared with each other:*
  - (a) *studies reporting more than one test*
  - (b) *microarray studies*
  - (c) *concordance.*

## Results: oncotype DX

### Development: oncotype DX

See *Report Supplementary Material 2* for a description of the development of oncotype DX.

## Prognostic performance: *oncotype DX*

### Study characteristics: *oncotype DX*

*Oncotype DX* was validated in 11 distinct data sets. Seven were reanalyses of RCTs [the National Surgical Adjuvant Breast and Bowel Project (NSABP) B14,<sup>49</sup> B20<sup>50</sup> and B28<sup>51,52</sup> trials; the Southwest Oncology Group (SWOG) trial 8814;<sup>53</sup> the Eastern Cooperative Oncology Group E2197<sup>54,55</sup> trial; UK patients from the TransATAC<sup>37,46</sup> trial; and a French trial, PACS01<sup>56</sup>] and four were retrospective cohort studies (one from the USA,<sup>57</sup> two from China<sup>58,59</sup> and one from Japan<sup>60</sup>). All studies recruited patients with either ER+ or HR+ tumours, but only TransATAC<sup>37,46</sup> and one Chinese study<sup>58</sup> recruited or reported a subgroup of exclusively HER2– patients. Two studies (TransATAC<sup>37,46</sup> and the SWOG 8814 trial)<sup>53</sup> recruited only postmenopausal patients.

The test was designed to predict outcomes in patients who received 5 years of endocrine therapy without chemotherapy. Only three studies treated patients with endocrine monotherapy, although it was not always clear if this was for 5 years; of these, one study recruited mixed lymph node status patients and reported separate analyses for LN0 and LN+ patients,<sup>37,46</sup> one recruited LN0 patients<sup>49</sup> and one recruited LN+ patients.<sup>53</sup> Of the remaining studies, one treated some patients with endocrine monotherapy and some with endocrine therapy and chemotherapy (LN0 patients<sup>50</sup>), two treated all patients with endocrine therapy and chemotherapy (one study recruited mixed lymph node status patients<sup>54,55</sup> and one recruited LN+ patients<sup>51,52</sup>) and one treated all patients with chemotherapy and some with endocrine therapy (LN+ patients).<sup>56</sup> The retrospective studies treated patients in accordance with usual practice (without *oncotype DX*) with varying levels of endocrine therapy and chemotherapy.<sup>57–60</sup> The total number of patients included was 4929. A detailed narrative synthesis of study characteristics is provided in *Report Supplementary Material 2*. Study characteristics data are presented in *Report Supplementary Material 2, Table 1*.

Two studies did not report how *oncotype DX* was conducted (PACS01 study<sup>56</sup> and Russell *et al.*<sup>57</sup>). In all but three other cases, the test was conducted on fixed, paraffin-embedded tissue by Genomic Health using the commercial *oncotype DX* assay. The three exceptions were the two studies from China in which the test was not carried out by Genomic Health<sup>58,59</sup> and the study by Paik *et al.*,<sup>49</sup> as Paik *et al.* (2006)<sup>50</sup> described the assay used in Paik *et al.* (2004)<sup>49</sup> as being ‘a preliminary version of the RT-PCR assay (lacking standardized reagents, calibrators, and controls)’. In these three studies, the equivalence of the tests to the commercially offered *oncotype DX* assay is unknown.

### Quality assessment: *oncotype DX*

Quality assessment is summarised in *Report Supplementary Material 2*. All studies were validation studies. Only three studies<sup>37,46,49,53</sup> used an appropriate study design, as eight<sup>50–52,54–59</sup> included patients who had been treated with chemotherapy or did not report the proportion of patients treated with chemotherapy. Undertreatment with endocrine therapy and overtreatment with chemotherapy both have the potential to affect recurrence and may alter the observed HRs for outcomes between risk groups. No studies included all eligible patients and only three<sup>37,46,53,54</sup> stated that they blinded test assessors to patient outcomes. A lack of blinding is likely to have a low impact as the test is objective. There are concerns about patient spectrum bias in all studies, mainly owing to the retrospective nature of the studies and the exclusion of tumour samples with insufficient tissue probably leading to the loss of patients with smaller tumours. The potential loss of patients with small tumours is of unknown concern, as it is unknown whether or not the test would have a different prognostic performance in these patients.

### Results: *oncotype DX*

The following is a summary of key results from the review. A detailed narrative synthesis of all study results is provided in *Report Supplementary Material 2*.

### Distribution of patients by risk group: oncotype DX

Data are presented in *Table 3*. The proportion of patients classified as being at low risk ranged from 48%<sup>60</sup> to 64%<sup>46</sup> in LNO cohorts and was generally lower, ranging from 36%<sup>51,52</sup> to 57%<sup>46</sup> in LN+ cohorts. The proportion of patients who were classified as being at intermediate risk ranged from 20%<sup>60</sup> to 27%<sup>46</sup> in LNO cohorts, and was generally higher in LN+ cohorts, ranging from 30%<sup>56</sup> to 34%<sup>51,52</sup>. The proportion of patients who were classified as being at high risk ranged from 9% to 33% in LNO patients and was similar among LN+ patients, ranging from 11% to 32%. The number of patients who are likely to be prescribed chemotherapy on the basis of their test results will, to a large extent, depend on how intermediate-risk patients are handled and whether or not they would be handled in the same way in the LNO and LN+ groups.

### Prognostic performance, unadjusted analyses: oncotype DX

Data are presented in *Table 3*. The 10-year DRFI rates in low-risk LNO patients treated with endocrine monotherapy ranged from 93% to 97% (three studies<sup>46,49,60</sup>), and was similar when 100% patients received endocrine therapy and chemotherapy (96%, one study<sup>50</sup>). LN+ patients had much lower 10-year DRFI rates: 82% (one study<sup>46</sup>) with endocrine monotherapy and 81% (one study<sup>51,52</sup>) when 100% of patients received endocrine therapy and chemotherapy. The 10-year DRFI rates in LNO intermediate-risk patients treated with endocrine monotherapy ranged from 86% to 100% (three studies<sup>46,49,60</sup>), and was similar when 100% of patients received endocrine therapy and chemotherapy (89%, one study<sup>50</sup>). LN+ intermediate-risk patients had much lower 10-year DRFI rates: 75% (one study<sup>46</sup>) with endocrine monotherapy and 65% (one study<sup>51,52</sup>) when 100% of patients received endocrine therapy and chemotherapy. The 10-year DRFI rates in LNO high-risk patients treated with endocrine monotherapy ranged from 70% to 77% (three studies<sup>46,49,60</sup>), and was higher when 100% of patients received endocrine therapy and chemotherapy (88%, one study<sup>50</sup>). LN+ high-risk patients treated with endocrine monotherapy had similar 10-year DRFI rates to LNO patients, at 69% (one study<sup>46</sup>); in studies in which all patients received endocrine therapy and some or all received chemotherapy, the DRFI was lower, at 56% (one study<sup>51,52</sup>). All the DRFI rates in this paragraph exclude one study from China, which appeared an outlier with very low DRFI rates (Sun *et al.*<sup>59</sup>). The study from Japan<sup>60</sup> also reported some unusual results in that intermediate-risk patients had better DRFI than low-risk patients (e.g. 10-year DRFI rate was 97% and 100%, respectively). It is unclear if, for both of these studies,<sup>59,60</sup> the unusual results are due to small sample sizes ( $n = 98$ <sup>59</sup> and  $n = 200$ <sup>60</sup>), differences in treatment practices in Japan and China compared with Western countries or differences in ethnicity.

Despite confounding from treatment, the studies reporting prognostic performance data reported largely statistically significant differences between high-risk and low-risk groups, whether through HRs or through analyses of event rates per group, and this was the case regardless of lymph node status. However, differences between the intermediate-risk group and the high- or low-risk groups were not always statistically significant, particularly in the LN+ population (see *Table 3*).

Two studies reported a C-index (AUC). One study<sup>54,55</sup> was in LN+/LNO patients and the other was in LNO patients.<sup>58</sup> In both cases, the C-index was 0.69, which indicated that the model was better than chance at placing patients into appropriate risk categories and nearly reaches the cut-off point for a 'good' test of 0.7.<sup>48</sup>

Data for OS, BCSS, RFS and RFI can be found in *Report Supplementary Material 2*. These data support observations for DRFS, DRFI and DFS.

### Additional prognostic value, adjusted analyses: oncotype DX

Data are presented in *Table 4*. The analyses that reported multivariable Cox proportional hazards models that were adjusted for clinicopathological variables generally indicated that the prognostic performance of oncotype DX had additional benefit over these factors, as HRs remained significant in most analyses (the exception being RFS and OS analyses by Toi *et al.*<sup>60</sup>). This was consistent regardless of lymph node status and variables adjusted for, which included age, tumour size and LN status (when applicable) in all cases and grade in most cases (Toi *et al.*<sup>60</sup> and Sun *et al.*<sup>59</sup> being the exceptions). However, covariates included in multivariate analyses varied, and it is not clear if all important covariates were included in all analyses.

TABLE 3 Oncotype DX prognostic performance: DRFS, DRFI and DFS

Reference (first author and year)	Cohorts	Population	Nodal status	ET/chemotherapy	Cut-off points	Percentage of patients per group			DRFS/DRFI/DFS: % risk of outcome (95% CI)						DRFS/DRFI/DFS: HR (95% CI)	
						Low	Intermediate	High	0–5 years			0–10 years			0–5 years	0–10 years
									Low	Intermediate	High	Low	Intermediate	High		
<b>DRFS<sup>a</sup></b>																
<i>LNO, variable ET and chemotherapy</i>																
Gong 2016 <sup>58</sup> (n = 153)	SYSMH, CCSYU and 3rd HNC	100% HR+, 100% HER2–	LNO	100% ET; 79% chemotherapy	NR	49	26	25							0–5 years:	
<ul style="list-style-type: none"> <li>High vs. low: 2.2 (1.11 to 4.30); p = 0.004</li> <li>High vs. intermediate: 1.9 (0.55 to 6.47); p = 0.108</li> <li>Intermediate vs. low: 1.0 (0.67 to 1.52); p = 0.953</li> <li>C-index (AUC) 0.685 (95% CI 0.540 to 0.830)</li> </ul>																
<b>DRFI</b>																
<i>LNO/+</i>																
<b>Variable ET and chemotherapy</b>																
Sun 2011 <sup>59</sup> (n = 93) <sup>a</sup>	HAAMMS	100% HR+, 86% HER2–	LN+/LNO	LN+/LNO, 75.3% ET, 80.6% chemotherapy	18–30	37	31	32	5.5 years median follow-up						5.5 years median follow-up, RS 50-point Difference: 2.35 (1.58 to 3.49); p < 0.001	
<ul style="list-style-type: none"> <li>Low vs. high: p &lt; 0.001</li> <li>Inter vs. high: p = 0.003</li> </ul>																
<i>LNO</i>																
<b>100% ET monotherapy</b>																
Paik 2004, <sup>49</sup> Tang 2011 <sup>61</sup> and Wolmark 2016 <sup>52</sup> (n = 668)	NSABP B-14	100% ER+, HER2+/HER2–, % NR	LNO	100% ET	18–30	51	22	27	97.9 (95.6 to 99.0) <sup>b</sup>	90.8 (84.7 to 94.5) <sup>b</sup>	77.9 (71.1 to 83.4) <sup>b</sup>	93.2 (90.4 to 96.0)	85.7 (79.7 to 91.7)	69.5 (62.6 to 76.4)	RS 50-point difference: 6.04 (3.88 to 9.41); p < 0.001 <sup>b</sup>	Intermediate vs. low: 2.21 (1.28 to 3.81) High vs. low: 3.8 (2.36 to 6.1); p < 0.001
Log rank p < 0.001 <sup>b</sup>																
p < 0.001 high vs. low																
5–10 years: 95.2 (92.1 to 97.2) <sup>b</sup>																
5–10 years: 94.4 (88.0 to 97.5) <sup>b</sup>																
5–10 years: 89.2 (82.4 to 93.4) <sup>b</sup>																
5–10 years: RS 50-point difference – 1.55 (0.81 to 2.97); p = 0.20 <sup>b</sup>																
Log rank p = 0.06 <sup>b</sup> high vs. low																
5–15 years: 93.3 (89.6 to 95.7) <sup>b</sup>																
5–15 years: 88.1 (79.9 to 93.1) <sup>b</sup>																
5–15 years: 86.4 (79.0 to 91.3) <sup>b</sup>																

Reference (first author and year)	Cohorts	Population	Nodal status	ET/chemotherapy	Cut-off points	Percentage of patients per group			DRFS/DRFI/DFS: % risk of outcome (95% CI)						DRFS/DRFI/DFS: HR (95% CI)	
						Low	Intermediate	High	0–5 years			0–10 years			0–5 years	0–10 years
									Low	Intermediate	High	Low	Intermediate	High		
Toi 2010 <sup>60</sup> (n = 200)	8 Japanese hospitals	100% ER+, HER2 NR	LNO	100% ET	18–30	48	20	33				96.7 (90.0 to 98.9)	100 (NR)	75.2 (62.2 to 84.3)		50-point increase: 6.20 (2.27 to 17.0); p < 0.001
Sestak 2017 <sup>46</sup> (data request) and Dowsett 2010 <sup>37</sup> (n = 829)	TransATAC	100% HR+, 100% HER2–, postmenopausal	LNO	100% ET	18–30	64	27	9	99.1 (NR)	94 (NR)	88.9 (NR)	94.9 (NR)	87.7 (NR)	77.2 (NR)	Intermediate vs. low: 6.37 (2.27 to 17.87)	Intermediate vs. low: 2.67 (1.53 to 4.68)
<b>100% ET+ chemotherapy</b>																
Paik 2006 <sup>50</sup> (n = 424)	NSABP B-20	100% ER+, HER2+/HER2–	LNO	100% ET and chemotherapy	18–30	51	21	28				95.6 (92.7 to 98.6)	89.1 (82.4 to 95.9)	88.1 (82.0 to 94.2)		
<b>Variable ET and chemotherapy</b>																
Sun 2011 <sup>59</sup> (n = 57) <sup>a</sup>	HAAMMS	100% HR+, 86% HER2–	LNO	75.3% ET, 80.6% chemotherapy	18–30	–	–	–	84.4 (77.2 to 91.6)	72.6 (62.1 to 83.1)	41.7 (27.5 to 55.9)	57.9 (41.4 to 74.4)	43.0 (23.7 to 62.3)	20.8 (4.4 to 37.2)		p = 0.02
<b>LN+</b>																
<b>100% ET monotherapy</b>																
Sestak 2017 <sup>46</sup> (data request) and Dowsett 2010 <sup>37</sup> (n = 219)	TransATAC	100% HR+, 100% HER2–, postmenopausal	LN1–3	100% ET	18–30	57	32	11	95.9 (NR)	84.8 (NR)	83.6 (NR)	81.8 (NR)	75.4 (NR)	68.6 (NR)	Intermediate vs. low: 3.84 (1.31 to 11.23)	Intermediate vs. low: 1.66 (0.86 to 3.23)
continued																

**TABLE 3** Oncotype DX prognostic performance: DRFS, DRFI and DFS (*continued*)

Reference (first author and year)	Cohorts	Population	Nodal status	ET/chemotherapy	Cut-off points	Percentage of patients per group			DRFS/DRFI/DFS: % risk of outcome (95% CI)						DRFS/DRFI/DFS: HR (95% CI)	
						Low	Intermediate	High	0–5 years			0–10 years			0–5 years	0–10 years
									Low	Intermediate	High	Low	Intermediate	High		
<b>Variable ET and chemotherapy</b>																
Wolmark 2016 <sup>52</sup> and Mamounas 2012 <sup>51</sup> (n = 1065)	NSABP-28	100% ER+, HER2 NR	LN+	100% chemotherapy and ET	18–30	36	34	30	91.6 (88.3 to 94.0)	81.2 (76.8 to 84.9)	70.3 (64.9 to 75.1)	80.9 (76.4 to 84.6) <sup>c</sup>	64.9 (59.6 to 69.7) <sup>c</sup>	55.8 (50.0 to 61.2) <sup>c</sup>	RS 50-point difference: 4.22 (2.93 to 6.07); p < 0.001	
									Log rank p < 0.001			p < 0.001				
									5–10 years: 88.3 (84.3 to 91.4)	5–10 years: 79.9 (74.7 to 84.2)	5–10 years: 79.3 (73.1 to 84.3)	5–10 years: RS 50-point Difference: 1.66 (1.05 to 2.61); p = 0.04				
									Log rank p = 0.02							
Penault- Llorca 2014 <sup>56</sup> (n = 530)	PACS01	100% HR+	LN+	100% chemotherapy, 74.2% ET	NR	39	30	31	93.7 (89.4 to 96.3)	87.3 (81.0 to 91.6)	69.3 (61.5 to 75.8)	p < 0.001			7.7 years median follow-up, RS 50- point difference: 4.1 (CI NR); p < 0.001	
Sun 2011 <sup>59</sup> (n = 35) <sup>a</sup>	HAAMMS	100% HR+, 86% HER2–	LN+	LN+/LN0, 75.3% ET, 80.6% chemotherapy	18–30				62.5 (45.4 to 79.6)	66.7 (51.0 to 82.4)	16.7 (7.9 to 25.5)	62.5 (45.4 to 79.6)	33.3 (8.5 to 58.1)	16.7 (7.9 to 25.5)	p = 0.038	
<b>DFS<sup>d</sup></b>																
<b>LN+</b>																
<b>100% ET monotherapy</b>																
Albain 2010 <sup>53</sup> (n = 148)	SWOG- 8814	100% HR+, 91% HER2–, postmenopausal	LN+, 100% LN > 3, 37%	100% ET	18–30	37	31	32	–	–	–	60	49	43	RS 50-point difference: 2.64 (1.33 to 5.27); p = 0.006	
															Assumption of proportional hazards not met (p = 0.0016)	
															0–5 years: HR 5.55 (2.32 to 3.28); p = 0.0002	
															5–10 years: HR 0.86 (0.27 to 2.74); p = 0.80	

Reference (first author and year)	Cohorts	Population	Nodal status	ET/chemotherapy	Cut-off points	Percentage of patients per group			DRFS/DRFI/DFS: % risk of outcome (95% CI)						DRFS/DRFI/DFS: HR (95% CI)	
						Low	Intermediate	High	0–5 years			0–10 years			0–5 years	0–10 years
									Low	Intermediate	High	Low	Intermediate	High		
<b>Variable ET and chemotherapy</b>																
Penault- Llorca 2014 <sup>56</sup> (n = 530)	PACS01	100% HR+	LN+	100% chemotherapy, 74.2% ET	NR	39	30	31	90.8 (86.0 to 94.1)	84.9 (78.3 to 89.6)	64.6 (56.7 to 71.4)					7.7 years median follow-up, RS 50- point difference: 3.3 (CI NR); p < 0.001
Wolmark 2016 <sup>52</sup> and Mamounas 2012 <sup>51</sup> (n = 1065)	NSABP-28	100% ER+, HER2 NR, menopausal status NR, female NR	LN+	100% chemotherapy and ET	18–30	36	34	30				75.8 (71.1 to 79.8)	57.0 (51.6 to 61.9)	48.0 (42.3 to 53.4)		
<i>LN status NR</i>																
<b>ET and chemotherapy NR</b>																
Russell 2016 <sup>37</sup> (n = 135)	University of South Florida and Morton Plan Hospital	100% ER+, HER2– NR, menopausal status NR, female NR	NR	NR – usual practice guided by MammaPrint	NR	53	26	21								4.5 years median follow-up: Mantel–Cox log-rank test
<ul style="list-style-type: none"> <li>• Intermediate vs. low: p = 0.760</li> <li>• High vs. low: p = 0.036</li> <li>• Intermediate vs. high: p = 0.072</li> </ul>																
3rd HNC, Third Hospital of Nanchang City; ET, endocrine therapy; HAAMMS, Hospital Affiliated Academy of Military Medical Science, Beijing; NR, not reported; RS, recurrence score; SYSMH, Sun Yat-sen Memorial Hospital (Cancer Centre of Sun Yat-sen University).																
a Outcome described as DRFS, but the definition is for DRFI as it excludes contralateral disease, locoregional relapse, other primary cancers and non-breast-cancer deaths.																
b From Wolmark <i>et al.</i> <sup>52</sup>																
c These data are from Mamounas <i>et al.</i> <sup>51</sup> The same data are reported in the company submission <sup>62</sup> as DRFS. As DRFI is defined and reported in Wolmark <i>et al.</i> , <sup>52</sup> we have assumed Mamounas <i>et al.</i> <sup>51</sup> is correct in calling this DRFI.																
d The definition of DFS is unclear for all studies.																

**TABLE 4** Oncotype DX: additional prognostic value over clinicopathological factors or comparator tests

Reference (first author and year)	Cohorts	Population	Nodal status	ET/chemotherapy	Cut-off point	Outcome	Test or comparator <sup>a</sup>	Multivariable Cox proportional hazards model (adjusted for clinicopathological factors <sup>b</sup> ): HR (95% CI) unless otherwise stated
<b>LN+/LN0, 100% ET and chemotherapy</b>								
Goldstein 2008 <sup>54</sup> and Sparano 2012 <sup>55</sup> (n = 465)	E2197 (ECOG trial)	100% HR+, 44% HER2-, premenopausal/postmenopausal	LN0, 56.5% LN1-3, 43.5%	All ET and chemotherapy, 40% aromatase inhibitor	18-30	RFI	Oncotype DX vs. clinicopathological factors <sup>a</sup>	5 year: <sup>54</sup> HR (RS 50-point difference): 2.12 (0.97 to 4.65, p = 0.06) <sup>b</sup> 3.13 (1.60 to 6.14, p = 0.0009) <sup>b</sup> 10 year: <sup>55</sup> HR (RS 50-point difference): 2.27 (1.04 to 4.97, p NR)
		100% HR+, 100% HER2-	NR				Oncotype DX vs. integrator based on AOL <sup>b</sup>	5 year: <sup>54</sup> for 50-point difference using central grade: <ul style="list-style-type: none"> <li>• RS HR: 2.51 (95% CI 1.71 to 3.70); p &lt; 0.001</li> <li>• Integrator HR: 1.51 (95% CI 1.07 to 2.13); p = 0.02</li> </ul> For 50-point difference using local grade: <ul style="list-style-type: none"> <li>• RS HR: 2.64 (95% CI 1.80 to 3.87); p &lt; 0.001</li> <li>• Integrator HR: 1.34 (95% CI 0.94 to 1.91); p = 0.11</li> </ul> Interaction term was not significant indicating effect of RS is largely independent of the level of the integrator 5 year: <sup>54</sup> C-index (AUC): <ul style="list-style-type: none"> <li>• RS: 0.69</li> <li>• Integrator (central grade): 0.61</li> <li>• Integrator (local grade): 0.56</li> </ul>
Sestak 2017 (data request) <sup>46</sup> and Dowsett 2010 <sup>37</sup> (n = 774)	TransATAC	100% HR+, 100% HER2-, postmenopausal	LN+/LN0	100% ET	18-30	DRFI	Oncotype DX vs. CTS Oncotype DX vs. NPI	Increase in likelihood ratio $\chi^2$ over comparator 10 year: 15.22 (p = 0.0001) 10 year: 11.89 (p = 0.0006)

Reference (first author and year)	Cohorts	Population	Nodal status	ET/chemotherapy	Cut-off point	Outcome	Test or comparator <sup>a</sup>	Multivariable Cox proportional hazards model (adjusted for clinicopathological factors <sup>b</sup> ): HR (95% CI) unless otherwise stated	
<b>LN0, 100% ET monotherapy</b>									
Paik 2004 <sup>49</sup> and Tang 2011 <sup>61</sup> (n = 668)	NSABP B-14	100% ER+, HER2+/ HER2-, % NR	LN0	100% ET	18–30	DRFI		Increase in likelihood ratio $\chi^2$ over clinical factors <sup>c</sup> or comparator	
							Oncotype DX vs. clinicopathological factors <sup>a</sup>	<ul style="list-style-type: none"> <li>Cox proportional hazards model 1: 33.7, <math>p &lt; 0.001</math></li> <li>Cox proportional hazards model 2: 15.2, <math>p &lt; 0.001</math></li> <li>Cox proportional hazards model 3:<sup>c</sup> NR</li> </ul>	
							DRFI	Multivariable Cox proportional hazards model (adjusted for clinicopathological factors <sup>b</sup> )	
Toi 2010 <sup>60</sup> (n = 200)	8 Japanese hospitals (unnamed)	100% ER+, HER2 NR, menopausal status NR, % female NR	LN0	100% ET	18–30	DRFI RFI RFS OS	Oncotype DX vs. AOL <sup>d</sup>	<ul style="list-style-type: none"> <li>AOL: 1.93 (1.27 to 2.91); <math>p = 0.002</math></li> <li>RS 50-point difference: 2.83 (1.91 to 4.18); <math>p &lt; 0.001</math></li> </ul>	
							Oncotype DX vs. AOL and clinicopathological factors <sup>b</sup>	<ul style="list-style-type: none"> <li>AOL: 0.86 (0.45 to 1.62); <math>p = 0.636</math></li> <li>RS: 2.37 (1.58 to 3.55); <math>p &lt; 0.001</math></li> </ul>	
							Oncotype DX vs. clinicopathological factors <sup>d</sup>	<ul style="list-style-type: none"> <li>RS 50-point difference: 6.03 (2.17 to 16.7); <math>p &lt; 0.001</math></li> <li>RS 50-point difference: 3.38 (1.32 to 8.69)</li> <li>RS 50-point difference: 2.09 (0.84 to 5.20)</li> <li>RS 50-point difference: 2.67 (0.93 to 7.62)</li> </ul>	
Sestak 2017 (data request) <sup>46</sup> and Dowsett 2010 <sup>37</sup> (n = 591)	TransATAC	100% HR+, 100% HER2-, postmenopausal	LN0	100% ET	18–30	DRFI		Increase in likelihood ratio $\chi^2$ over comparator	
							Oncotype DX vs. CTS	5 year: 10.03 ( $p = 0.002$ )	10 year: 10.64 ( $p = 0.001$ )
							Oncotype DX vs. NPI	5 year: 9.62 ( $p = 0.002$ )	10 year: 8.82 ( $p = 0.003$ )

continued

**TABLE 4** Oncotype DX: additional prognostic value over clinicopathological factors or comparator tests (*continued*)

Reference (first author and year)	Cohorts	Population	Nodal status	ET/chemotherapy	Cut-off point	Outcome	Test or comparator <sup>a</sup>	Multivariable Cox proportional hazards model (adjusted for clinicopathological factors <sup>b</sup> ): HR (95% CI) unless otherwise stated
<b>LN0, variable ET and chemotherapy</b>								
Sun 2011 <sup>59</sup> (n = 57)	HAAMMS	100% HR+, 86% HER2- (7.5% unclear)	LN0	75.3% ET, 80.6% chemotherapy	18–30	DRFS	RS (not Genomic Health) vs. clinicopathological factors <sup>c</sup>	RS 1-point difference: 1.03 (1.01 to 1.06); <i>p</i> = 0.017
<b>LN+, variable ET and chemotherapy</b>								
Penault-Llorca 2014 <sup>56</sup> (n = 530)	PACS01	100% HR+	LN+	100% chemotherapy, 74.2% ET	NR	NR, assume DRFI	Oncotype DX vs. clinicopathological factors <sup>a</sup>	<i>p</i> < 0.001
Sun 2011 <sup>59</sup> (n = 35)	HAAMMS	100% HR+, 86% HER2- (7.5% unclear)	LN+	75.3% ET, 80.6% chemotherapy	18–30	DRFS	RS (not Genomic Health)	RS 1-point difference: 1.03 (1.00 to 1.07); <i>p</i> = 0.039
Sestak 2017 (data request) <sup>46</sup> and Dowsett 2010 <sup>37</sup> (n = 183)	TransATAC	100% HR+, 100% HER2-, postmenopausal	LN+	100% ET	18–30	DRFI	Oncotype DX vs. CTS Oncotype DX vs. NPI	Increase in likelihood ratio $\chi^2$ over comparator 5 year: 3.29 ( <i>p</i> = 0.07) 10 year: 3.56 ( <i>p</i> = 0.06) 5 year: 2.47 ( <i>p</i> = 0.1) 10 year: 2.14 ( <i>p</i> = 0.1)
Wolmark 2016 <sup>52</sup> and Mamounas 2012 <sup>51</sup> (n = 1065)	NSABP-28	100% ER+, HER2 NR, menopausal status NR, female NR	LN+	100% chemotherapy and ET	18–30	DFS, DRFI, OS	Oncotype DX vs. clinicopathological factors <sup>a</sup>	<i>p</i> < 0.001

ECOG, Eastern Cooperative Oncology Group; ET, endocrine therapy; HAAMMS, Hospital Affiliated Academy of Military Medical Science, Beijing; RS, oncotype DX recurrence score.

a Adjusted for:

- Goldstein *et al.*<sup>54</sup> – number positive nodes, tumour size, age, HER2 status, grade.
- Paik *et al.*<sup>49</sup> – Cox proportional hazards model 1 adjusted for age and tumour size; Cox proportional hazards model 2 adjusted for age, tumour size, tumour grade, HER2 amplification, amounts of oestrogen and progesterone-receptor protein; Cox proportional hazards model 3 adjusted for age, tumour size, grade.
- Penault-Llorca *et al.*<sup>56</sup> – treatment, age, tumour size and grade, number of positive nodes, surgery type and Ki-67 status.
- Sun *et al.*<sup>59</sup> – unclear if all clinicopathological factors kept in the analysis: age, tumour size, nodal status, ER, PR, HER2, ET, chemotherapy, St Gallen criteria,<sup>63</sup> RS.
- Toi *et al.*<sup>60</sup> – age and clinical tumour size.
- Wolmark *et al.*<sup>52</sup>/Mamounas *et al.*<sup>51</sup> – does not specify which covariates were included for which outcomes, but selected from treatment, age, tumour size, tumour grade, number of positive nodes and type of surgery.

b First Cox proportional hazards model used centrally determined disease grade, second Cox proportional hazards model used locally determined disease grade.

c Reported in Tang *et al.*<sup>44</sup>

d In this analysis, the Cox proportional hazards model only included oncotype DX and an integrator based on AOL, where the integrator was adjusted to 5-year outcomes rather than AOL's 10-year outcomes.

The use of the 50-point difference in the adjusted analyses of prognostic performance indicated that the recurrence score may be prognostic over clinicopathological factors, but does not provide information about the clinical significance of the 18–30 recurrence score cut-off points.

The likelihood ratio  $\chi^2$  in the TransATAC data set was statistically significantly higher for *oncotype* DX than for CTS or NPI only for LN0 patients [10-year DRFI likelihood ratio  $\chi^2$  10.64 ( $p = 0.001$ ) and 8.82 ( $p = 0.003$ ), respectively], while the difference was not statistically significant for LN+ patients [3.56 ( $p = 0.06$ ) and 2.14 ( $p = 0.1$ ), respectively].<sup>46</sup> Compared with AOL, and with a model based on AOL but with 5-year outcomes, *oncotype* DX also appeared to provide additional prognostic information (see *Table 4*).<sup>49,61</sup>

### **Oncotype DX RSPC**

Data are presented in *Table 5*. One study (Tang *et al.*<sup>44</sup>) derived the RSPC score in a meta-analysis of NSABP B-14 and TransATAC (LN+/LN0;  $n = 1735$ ), and performed a limited validation in NSABP B-20 (LN0;  $n = 625$ ), which included 233 patients used to derive the *oncotype* DX recurrence score. For this reason, both NSABP B-14 and B-20 data were used to derive part of the algorithm. Based on the NSABP B-14 analysis set, the *oncotype* DX RSPC algorithm (*oncotype* DX plus age, tumour size and grade) appeared to provide additional prognostic information over *oncotype* DX and over clinicopathological variables, and was able to classify more patients into a low-risk category than *oncotype* DX while maintaining a roughly equivalent rate of distant recurrence in the low-risk group. In the NSABP B-20 cohort, RSPC had prognostic value in a univariate analysis.

### **Conclusion: *oncotype* DX and RSPC prognostic performance**

Seven reanalyses of RCTs and four retrospective cohort studies were included, with a total of 4929 patients. The generalisability of the evidence base to the decision problem is uncertain owing to the loss of patients with insufficient tumour samples. Generally, when comparing LN0 patients with LN+ patients, similar numbers were at high risk, but more were at low risk in LN0 cohorts, and more at intermediate risk in LN+ cohorts. How many patients would be prescribed chemotherapy would depend in large part on how intermediate patients are handled. The 10-year DRFI rates suggest that patients in the LN0 low-risk group<sup>46,49,60</sup> are at very low ROR (10-year DRFI range 93–97%) in the absence of chemotherapy, and patients in the intermediate risk group may be at somewhat higher risk (10-year DRFI range 86–100%). In the LN+ study using endocrine monotherapy, patients were generally at higher risk of recurrence than LN0 patients in both the low and the intermediate categories (10-year DRFI  $< 85\%$  and  $\leq 75\%$ , respectively). Unadjusted analyses indicated that *oncotype* DX had prognostic power (statistically significant differences between low-risk and high-risk groups) across various recurrence outcomes, regardless of lymph node status. HRs between the intermediate-risk group and the high- or low-risk groups were not always statistically significant. *Oncotype* DX provided additional prognostic information over the most commonly used clinicopathological variables (age, grade, size and nodal status) regardless of lymph node status (although it was not always clear if all relevant variables had been included in the analyses), and over CTS and NPI in LN0 (but not LN+) patients. On the basis of proportions classified as low risk and DRFI rates, RSPC may outperform *oncotype* DX in LN0 patients, but these data are from the derivation cohort, with only limited validation data from a cohort (NSABP B-20) that included patients who were used to derive one of its constituent parts (*oncotype* DX Breast Recurrence Score), and it has not been tested in premenopausal or LN+ patients.

### **Chemotherapy benefit: *oncotype* DX**

Chemotherapy benefit relates to the ability of the test to predict which patients will respond to chemotherapy, and can be assessed by considering whether or not the effect of chemotherapy versus no chemotherapy on patient outcomes differs in accordance with the test score (e.g. by comparing HRs or  $p$ -values between risk groups). Formal assessments of chemotherapy benefit include interaction tests that assess whether or not the difference is statistically significant. The results of the review are summarised here, and a full narrative synthesis is provided in *Report Supplementary Material 3*.

**TABLE 5** Oncotype DX RSPC, discrimination, reclassification and additional prognostic value

Reference (first author and year)	Cohorts	Population	Nodal status	ET/chemotherapy	Cut-off point	Outcome	Test	% of patients per group			Discrimination			HR, <i>p</i> -value	Reclassification	Additional prognostic value, difference in likelihood ratio $\chi^2$	
								Low risk	Intermediate risk	High risk	Low risk	Intermediate risk	High risk				
<b>Node negative and node positive</b>																	
Tang 2011 <sup>44</sup>	NSABP, B-14 and TransATAC meta-analysed	ER+, HER2+/HER2-, % NR	LN0 (B-14); LN+/LN0 (TransATAC)	100% ET	12–20% risk	DRFI 10 years	RSPC	64	18	18	93.5 (91.5 to 95.5)	82.4 (77.1 to 87.7)	73.8 (68.4 to 79.2)	HR/CI NR, <i>p</i> < 0.001 with increasing risk group	RSPC vs. RS: DRFI risks not significantly different between RS and RSPC within each risk group ( <i>p</i> = 0.68, <i>p</i> = 0.27 and <i>p</i> = 0.42 for low-, intermediate- and high-risk groups)	RSPC vs. oncotype DX RS: 76.9, <i>p</i> < 0.001	
							RS	54	27	19	94.1 (92.2 to 96.0)	86.2 (81.9 to 90.5)	70.5 (63.4 to 76.5)	HR/CI NR, <i>p</i> < 0.001 with increasing risk group	RSPC vs. grade, tumour size, age: 45.4, <i>p</i> < 0.001		
															RS intermediate-risk patients ( <i>n</i> = 272):		
															<ul style="list-style-type: none"> <li>16.9% high-risk RSPC</li> <li>55.1% low-risk RSPC</li> </ul>		
															RS low-risk patients ( <i>n</i> = 783):		
															<ul style="list-style-type: none"> <li>1.9% high-risk RSPC</li> <li>8.9% intermediate-risk RSPC</li> </ul>		
															RS high-risk patients ( <i>n</i> NR):		
															<ul style="list-style-type: none"> <li>28.6% intermediate-risk RSPC</li> <li>Other differences NR</li> </ul>		
	NSABP and B-20	ER+, HER2+/HER2-, % NR	LN0	100% ET; 64% chemotherapy			RSPC								RSPC: 2.43, <i>p</i> < 0.001		
															RS: 2.22, <i>p</i> < 0.001		

ET, endocrine therapy; LN, lymph node; NR, not reported; RS, oncotype DX recurrence score.

## Study design and patient characteristics

Five data sets, reported across 10 published references<sup>44,50,53,61,64–69</sup> and one academic-in-confidence (AiC) manuscript (see *Report Supplementary Material 3, Table 3*), have conducted analyses that assess the ability of *oncotype* DX to predict the benefit of chemotherapy. Two were reanalyses of RCTs: the American (NSABP) B-20 study ( $n = 651$ ) in LN0 was reported by Paik *et al.*,<sup>50</sup> Tang *et al.*<sup>61</sup> and Tang *et al.*;<sup>44</sup> and the American SWOG 8814 study ( $n = 367$ ) in LN+ patients (38% had four or more lymph nodes) was reported by Albain *et al.*<sup>53</sup> In both trials, patients were randomised to tamoxifen only, or tamoxifen plus cyclophosphamide. NSABP-B20 did not select participants by *HER2* status, but an analysis of *HER2*– patients was provided as a personal communication (Professor Tang via NICE, University of Pittsburgh, personal communication, February 2018) as part of the NICE assessment process. SWOG-8814<sup>53</sup> recruited patients with any *HER2* status (12% were *HER2*+) and all patients were postmenopausal. Both reanalyses had high attrition rates (72% and 60%, respectively), owing to missing clinical variables, missing samples, insufficient tissue and test failures.

The three remaining studies were observational<sup>64–67,70</sup> (total approximately 44,000 with some double-counting). Two LN0 studies were from the USA [MD Anderson Center,  $n = 1424$ ;<sup>64,65</sup> Surveillance, Epidemiology, and End Results (SEER) registry,  $n = 40,134$ <sup>67</sup>] and one study recruiting a mix of LN+ and LN0 patients was from Israel [Clalit Health Services one lymph node micrometastasis (LN1micro)–LN3,  $n = 620$ ; LN0–LN1micro,  $n = 1594$ <sup>66</sup>]. Additional analyses were provided to the EAG as AiC data but cannot be reported here. Patients were treated in accordance with local routine practice in conjunction with their *oncotype* DX score.

## Quality assessment

*Report Supplementary Material 3, Table 4*, presents the quality assessment of the included studies. Among the RCTs, neither trial scored well on every item. The key concerns included the use of the derivation cohort in Paik *et al.*<sup>50</sup>/Tang *et al.*<sup>61</sup> and high attrition rates in both trials. The comparison of baseline characteristics between patients included in the analysis and those excluded from the analysis showed differences in patient age at recruitment (Paik *et al.*<sup>49</sup>) and tumour grade. (Paik *et al.*<sup>50</sup>).

The three observational studies<sup>64–67,69</sup> are limited by their non-randomised design, whereby patients who received chemotherapy are likely to be systematically different in terms of known (and potentially unknown) prognostic variables (e.g. age) and treatment effect modifiers to those who did not, leading to a high risk of confounding. They also only recruited patients for whom an *oncotype* DX test had been ordered and it is unclear how this may have affected the patient spectrum and generalisability to the decision problem. However, owing to their prospective use of the test in clinical practice, three studies blinded the test assessors to the long-term outcomes.<sup>64–69</sup>

## Results

Both RCT reanalysis studies showed that unadjusted HRs for the effect of chemotherapy versus no chemotherapy on survival and recurrence outcomes were most favourable in the higher-risk groups. HRs were generally statistically significant in high-risk groups but not in low- or intermediate-risk groups. In the B20 study (LN0 patients),<sup>44,50,61</sup> unadjusted HRs for 10-year DRFI in the low-, intermediate- and high-risk groups were 1.31, 0.61 and 0.26, respectively. HRs restricted to *HER2*– patients (adjusted and unadjusted) showed the same pattern (*Table 6*; Professor Tang, personal communication). However, it is interesting to note that absolute differences (for chemotherapy vs. no chemotherapy) were very small in the low- and intermediate-risk groups (1.1% and 1.8%, respectively, both favouring no chemotherapy), although they were greater in the high-risk group (27.6% favouring chemotherapy).

In SWOG-8814 (LN+),<sup>53</sup> DRFI was not reported. HRs for 10-year DFS for low-, intermediate- and high-risk groups, adjusted for number of positive nodes, were 1.02, 0.72 and 0.59, respectively.

Unadjusted interaction tests were statistically significant for 10-year DRFI and OS in NSABP B-20 (LN0) ( $p = 0.031$  and  $p = 0.011$ , respectively).<sup>50,61</sup> Albain *et al.*<sup>53</sup> (LN+) found that the effect of recurrence score on treatment varied over time and that recurrence score is a treatment effect modifier in the first 5 years (interaction  $p$ -value 0.029) but not after 5 years (interaction  $p$ -value 0.580).

**TABLE 6** The prediction of chemotherapy responsiveness by oncoType DX: reanalyses of RCT data

Study	Outcome	% recurrence free, absolute benefit			HR for chemotherapy vs. no chemotherapy (95% CI)			Interaction tests	
		Low	Intermediate	High	Low	Intermediate	High	Unadjusted	Adjusted
NSABP-B20: LN0, ER+ (n = 651)  Paik 2006, <sup>50</sup> Tang 2011 <sup>61</sup> and Professor Tang, personal communication	<b>10-year DRFI unadjusted, HER2- unadjusted, HER2- adjusted<sup>a</sup></b>	Chemotherapy: 95.6%	Chemotherapy: 89.1%	Chemotherapy: 88.1% No chemotherapy: 60.5%	1.31 (0.46 to 3.78); p = 0.61	0.61 (0.24 to 1.59); p = 0.39	<b>0.26 (0.13 to 0.53); p &lt; 0.001</b>	Interaction (continuous RS) p = 0.031 or p = 0.038 (Tang 2011 <sup>61</sup> and Paik 2006 <sup>50</sup> )	Interaction <sup>a</sup> (continuous RS) adjusted for age, tumour size, grade, ER and PR:  ● All patients: <b>p = 0.035, 0.039, 0.068<sup>b</sup></b> ● HER2-: <b>p = 0.007, 0.018, 0.022<sup>b</sup></b>
	<b>10-year DFS</b>	No chemotherapy: 96.8%	No chemotherapy: 90.9%	Absolute difference: 27.6%	1.21 (0.41 to 3.55); p = 0.73	0.78 (0.29 to 2.11); p = 0.62	<b>0.21 (0.08 to 0.53); p &lt; 0.001</b>		
	<b>10-year OS</b>	Absolute difference: 1.1%	Absolute difference: 1.8%		1.18 (0.40 to 3.53); p = 0.76 <sup>d</sup>	0.67 (0.24 to 1.87); p = 0.44 <sup>d</sup>	<b>0.20 (0.07 to 0.52); p = 0.001<sup>a</sup></b>		
SWOG-8814: LN+, HR+, HER2+/HER2- (n = 367)  Albain 2010 <sup>53</sup>	<b>10-year DFS</b>	Chemotherapy: 64%		Chemotherapy: 55% No chemotherapy: 43%	1.02 (0.54 to 1.93); p = 0.97 <sup>c</sup>	0.72 (0.39 to 1.31); p = 0.48 <sup>c</sup>	0.59 (0.35 to 1.01); <b>p = 0.033<sup>c</sup></b>	Interaction (continuous RS) adjusted for positive nodes:  ● All years: p = 0.053 <sup>c</sup> ● 0–5 years: <b>p = 0.029<sup>c</sup></b> ● 5–10 years: p = 0.58 <sup>c</sup>	
	<b>0- to 5-year DFS</b>	No chemotherapy: 60%		Absolute difference: 12%					
	<b>5- to 10-year DFS</b>	Absolute difference: 4%			1.34 (0.47, 3.82) <sup>c</sup>	0.95 (0.43, 2.14) <sup>c</sup>	0.59 (0.32, 1.11) <sup>c</sup>		
	<b>10-year BCSS</b>			Chemotherapy: 73% No chemotherapy: 54% Absolute difference: 19%	p = 0.56	p = 0.89	<b>p = 0.033<sup>c</sup></b>		
	<b>10-year OS</b>			Chemotherapy: 68% No chemotherapy: 51% Absolute difference: 17%	1.18 (0.55 to 2.54); p = 0.68 <sup>c</sup> p = 0.63 log-rank	0.84 (0.40 to 1.78); p = 0.65 <sup>c</sup> p = 0.85 log-rank	0.56 (0.31 to 1.02); p = 0.057 <sup>c</sup> <b>p = 0.027</b> log-rank		

NR, not reported; P53, tumour protein p53; RS, recurrence score.

a Adjusted for age, tumour size, grade, ER and PR.

b p-values correspond to analyses using different assessments of tumour grade.

c Adjusted for number of positive nodes (1–3 vs. ≥ 4).

**Note**

Bold font denotes statistically significant analyses.

Interaction tests adjusted for clinicopathological factors in NSABP-B20 were borderline significant for the full cohort for DRFI ( $p = 0.035$ ,  $p = 0.039$  and  $p = 0.068$  for different methods of assessing tumour grade),<sup>50</sup> (Professor Tang, personal communication), whereas for the HER2- subgroup, the equivalent analyses were statistically significant ( $p = 0.007$ ,  $p = 0.018$  and  $p = 0.022$ ) (Professor Tang, personal communication). The EAG report<sup>71</sup> stated that it was unclear whether or not all factors were adjusted for simultaneously in B20; however, a personal communication with the biostatistician (Professor Tang, personal communication) confirmed that this was the case. Interaction tests in SWOG-8814 adjusted individually for each of age, ethnicity, tumour size, grade, PR, P53 and *HER2* were also statistically significant ( $p =$  not reported). Initially, the EAG interpreted this as a model including all clinicopathological variables; however, clarification from the authors in a personal communication (Professor Barlow, University of Washington School of Public Health, personal communication, March 2018) stated that each variable was included in a separate model. An interaction test adjusted for Allred-scored ER status was not significant ( $p = 0.15$ ). No interaction test that included all clinicopathological variables together was available.

The *oncotype* DX cut-off point below which chemotherapy could be avoided was reported to be approximately 20 in SWOG-8814,<sup>53</sup> but NSABP B-20 authors could not determine a cut-off point as there was no point below which chemotherapy did not confer an advantage.<sup>50,61</sup>

The analyses and available data were subject to some criticisms in the context of this decision problem. First, it was not clear whether or not all stratification factors used in randomising patients to treatment were included in the interaction test model. Second, categorising the continuous *oncotype* Breast Recurrence Score into risk groups may lead to loss of information and has the potential to create spurious interactions between recurrence score and chemotherapy benefit due to imbalances in clinicopathological variables between risk groups. Third, none of the analyses were conducted in the clinically-intermediate-risk patient group of interest to the decision problem; in particular, it is plausible that even if there is no chemotherapy benefit for clinically-low, *oncotype* DX-low patients, there could be benefit for clinically-intermediate (NPI of  $> 3.4$ ) *oncotype* DX-low patients. Fourth, patients from the no-chemotherapy arm of the B20 study were used to derive the *oncotype* DX score. Therefore, *oncotype* DX may be overfitted in this study arm (i.e. recurrence rates may be artificially low in *oncotype* low-risk patients and artificially high in *oncotype* DX high-risk patients). This could lead to an overestimate of chemotherapy benefit because the chemotherapy arm was not used in derivation; therefore, recurrence rates in this arm may show less separation between the low- and high-risk groups. A more thorough discussion of this and other quality issues is provided in *Report Supplementary Material 3*.

Other potential biases in the reanalyses of RCTs included attrition of samples, exclusion of patients owing to missing data for covariates and inclusion of HER2+ patients (applies only to SWOG-8814 LN+ patients), who are out of the scope of this assessment.

### Observational studies: results

Data are presented in *Table 7*. From the three observational cohort studies,<sup>64–67,69,70</sup> evidence was mixed and at high risk of confounding, because patients who received chemotherapy were likely to be at higher risk of recurrence than patients who did not. Only one study reported an interaction test between recurrence score categories and chemotherapy treatment, and this was statistically significant ( $p = 0.03$ ), but only adjusted for grade, tumour size, age and race (omitting ER and PR),<sup>67,70</sup> and for recurrence score as a continuous variable ( $p < 0.001$ ). The other two studies only reported HRs for chemotherapy versus no chemotherapy in intermediate- and high-risk patients,<sup>64–66,69</sup> and in one study these were statistically non-significant, even after adjustment for confounders.<sup>64,65</sup> In the other study,<sup>66,69</sup> patients with LN0/LN1micro did not appear to receive benefit from chemotherapy in the intermediate group (DRFI for chemotherapy vs. no chemotherapy: 94.4% vs. 94.7%, respectively), whereas those in the high-risk group did (DRFI for chemotherapy vs. no chemotherapy: 86.7% vs. 78.9%, respectively). In the LN1micro–LN3 subgroup, patients did appear to receive benefit from chemotherapy in the intermediate-risk group (DRFI for chemotherapy vs. no chemotherapy: 97.8% vs. 90.4%, respectively); data for high risk patients were not reported. A more detailed narrative is provided in *Report Supplementary Material 3*.

**TABLE 7** The prediction of chemotherapy responsiveness by oncotype DX: observational studies

Reference (first author and year)	Study	Outcome	Cut-off point	Prediction of chemotherapy benefit: chemotherapy vs. no chemotherapy			Additional predictive value, adjusted HR, chemotherapy vs. no chemotherapy (95% CI)			
				Low RS	Intermediate RS	High RS	Low RS	Intermediate RS	High RS	
Barcnas 2017 <sup>64</sup> Le Du 2015 <sup>65</sup> Median follow-up: 58 months HR+, HER2-, LNO, Stage I-II, had oncotype DX test All risk groups, all years: <i>n</i> = 1424 Diagnosed 2005 to 2011 and included in K-M analysis: <ul style="list-style-type: none"> <li>Intermediate RS: <i>n</i> = 547</li> <li>High RS: <i>n</i> = 142</li> </ul>	MD Anderson Center, USA	5-year DRFS	11–25	NR	Actuarial 5-year rate:	HR NR, <i>p</i> = 0.74	NR	1.25 (0.32 to 4.92); <i>p</i> = 0.746 <sup>a</sup>	0.67 (0.16 to 2.78); <i>p</i> = 0.584 <sup>a</sup>	
			18–30	NR	NR	NR	NR, too few events	0.80 (0.23 to 2.71); <i>p</i> = 0.716	0.32 (0.07 to 1.47); <i>p</i> = 0.143	
		5-year DRFS <sup>b</sup>	18–30	NR	Stage 1 disease, intermediate risk (RS 18–30) only <sup>b</sup> (HRs NR):	NR	NR	NR	NR	NR
					<ul style="list-style-type: none"> <li>pT1a (<i>n</i> = 13), NR</li> <li>pT1b (<i>n</i> = 95) <i>p</i> = 0.752</li> <li>pT1c (<i>n</i> = 246)</li> </ul> <p><i>p</i> = 0.020</p>					
		5-year IDFS	11–25	NR	Actuarial 5-year rate:	HR NR, <i>p</i> = 0.56	NR	1.64 (0.73 to 3.71); <i>p</i> = 0.233 <sup>a</sup>	0.67 (0.21 to 2.07); <i>p</i> = 0.483 <sup>a</sup>	
			18–30	NR	NR	NR	1.09 (0.14 to 8.62, <i>p</i> = 0.938)	0.78 (0.34 to 1.80); <i>p</i> = 0.571	0.50 (0.13 to 2.02); <i>p</i> = 0.334	
5-year RFS	11–25	NR	Actuarial 5-year rate:	HR NR, <i>p</i> = 0.94		1.46 (0.41 to 5.23); <i>p</i> = 0.564 <sup>a</sup>	0.78 (0.17 to 3.52); <i>p</i> = 0.748 <sup>a</sup>			
	18–30	NR	NR	NR	NR, too few events	0.98 (0.32 to 3.06); <i>p</i> = 0.975	NR			

Reference (first author and year)	Study	Outcome	Cut-off point	Prediction of chemotherapy benefit: chemotherapy vs. no chemotherapy			Additional predictive value, adjusted HR, chemotherapy vs. no chemotherapy (95% CI)		
				Low RS	Intermediate RS	High RS	Low RS	Intermediate RS	High RS
Stemmer 2016 <sup>66</sup> Stemmer 2016 <sup>69</sup> Median follow-up: 6 years ER+, HER2-, had oncoType DX test N0/1micro: n = 1594 LN1micro-LN3: n = 627 <sup>e</sup>	Clalit Health Services, <sup>66</sup> Israel	5-year OS <sup>c</sup>	11-25	NR	Actuarial 5-year rate: <ul style="list-style-type: none"><li>Chemotherapy 98% (95% CI 91% to 99%)</li><li>No chemotherapy 98% (95% CI 96% to 99%)</li></ul> HR NR, p = 0.91	HR NR, p = 0.18	NR	2.19 (0.44 to 11.0); p = 0.340 <sup>z</sup>	0.28 (0.04 to 2.05); p = 0.209 <sup>z</sup>
			18-30	NR	NR	NR	NR, too few events	0.86 (0.15 to 4.91); p = 0.861	0.13 (0.01 to 1.30); p = 0.082
		5-year DRF <sup>d</sup>	18-30	NR	LN0/1micro: <ul style="list-style-type: none"><li>Chemotherapy (38%): 94.4%</li><li>No chemotherapy (62%): 94.7%</li></ul>	LN0/1micro:	NR	NR	NR
			18-30	NR	LN1micro-LN3 (% DRF): <ul style="list-style-type: none"><li>Chemotherapy (40%): 97.8%</li><li>No chemotherapy (60%): 90.4%</li></ul>	LN1micro-LN3:	NR	NR	NR
		5-year BCSS <sup>d</sup>	11-25	NR	LN1micro-LN3 (% DRF): <ul style="list-style-type: none"><li>Chemotherapy (18%): 97.3%</li><li>No chemotherapy (82%): 95.9%</li></ul>	LN1micro-LN3:	NR	NR	NR
			18-30	NR	LN1micro-LN3: <ul style="list-style-type: none"><li>Chemotherapy (40%): 98.9%</li><li>No chemotherapy (60%): 96.3%</li></ul>	LN1micro-LN3:	NR	NR	NR
			11-25	NR	LN1micro-LN3: <ul style="list-style-type: none"><li>Chemotherapy (18%): 100%</li><li>No chemotherapy (82%): 98.8%</li></ul>	LN1micro-LN3:	NR	NR	NR

continued

**TABLE 7** The prediction of chemotherapy responsiveness by onco<sup>type</sup> DX: observational studies (*continued*)

Reference (first author and year)	Study	Outcome	Cut-off point	Prediction of chemotherapy benefit: chemotherapy vs. no chemotherapy			Additional predictive value, adjusted HR, chemotherapy vs. no chemotherapy (95% CI)		
				Low RS	Intermediate RS	High RS	Low RS	Intermediate RS	High RS
Petkov 2016 <sup>70</sup>	SEER registry, USA	Actuarial 5-year BCSS <sup>c</sup>	18–30	NR					Multivariable model <sup>g</sup> including chemotherapy treatment: RS remained significantly prognostic for 5-year BCSS for both chemotherapy-treated and untreated (or unknown) patients, but strength of association between RS categories and BCSS attenuated for those with chemotherapy reported as 'yes' ( $p = 0.03$ for covariate-adjusted interaction) vs. those reported as 'no/unknown'. Similar analysis with RS as continuous variable also significant both with and without adjustment for covariates ( $p < 0.001$ for both)
Roberts 2016 <sup>67</sup>									
Roberts 2017 <sup>68</sup>									
Follow-up: 38 months									
HR+, HER2-, LN0 <sup>f</sup>									
$n = 40,134$									

BCSM, breast cancer specific mortality; DR, distant recurrence; K–M, Kaplan–Meier; LN, lymph node; NR, not reported; pT, pathological tumour stage; RS, onco<sup>type</sup> DX recurrence score.

a Adjusted for age at diagnosis, tumour size, grade, histological subtype, LVI, type of surgery and endocrine therapy. Covariates producing unstable estimates were removed. Ki-67 was removed owing to too many missing values.

b Data from Le Du *et al.*,<sup>65</sup> in which only stage I disease patients were included; 17 intermediate patients were also in the TAILORx study.<sup>22</sup>

c OS and BCSS data do not meet the inclusion criteria as follow-up was  $< 5$  years.

d Converted to DRFI from DR; converted to BCSS from BCSM.

e Note overlap between LN0–1micro and LN1micro–LN3 analyses.

f HR+ by onco<sup>type</sup> DX and by IHC; HER2 status by onco<sup>type</sup> DX.

g Adjusted for grade, tumour size, age and race.

## RSPC results

Recurrence score–pathology–clinical results were derived in TransATAC and NSABP B-14,<sup>44</sup> and validated in NSABP B-20.<sup>44</sup> Only LNO data were available. An interaction test was non-significant ( $p = 0.10$ ), with a standardised HR of 0.65 (95% CI 0.39 to 1.09) (data not tabulated).<sup>44</sup>

In practice, it is unlikely that chemotherapy decisions would be made on *oncotype* DX scores independent of clinicopathological variables. Evidence relating to the ability of the test to predict chemotherapy benefit over and above routinely collected clinicopathological variables was provided in both RCT data sets in the adjusted interaction tests.<sup>50,53,61</sup> Interestingly, Tang *et al.*<sup>61</sup> tested the ability of AOL to predict benefit from chemotherapy in a large cohort of 1952 patients, and found it to have predictive ability for OS. However, the inclusion of clinicopathological variables alongside recurrence score in the RSPC algorithm resulted in a loss of predictive ability ( $p = 0.10$ ), indicating that the incorporation of clinicopathological factors may reduce prediction of chemotherapy benefit; therefore, if chemotherapy decisions are based on an informal consideration of clinicopathological factors alongside the *oncotype* DX score, this may reduce any predictive ability of *oncotype* DX in clinical practice.

## Conclusion: *oncotype* DX and RSPC chemotherapy benefit

In conclusion, there is some evidence from two reanalyses of RCTs to suggest that *oncotype* DX may predict benefit from chemotherapy, and that benefit from chemotherapy is highest in *oncotype* DX high-risk patients. Unadjusted interaction tests between *oncotype* DX risk group and chemotherapy benefit were mainly statistically significant. Adjusted interaction tests were borderline significant in the LNO NSABP B20 study (significant in HER2– patients), whereas in the LN+ SWOG-8814 study they were significant when adjusted for some clinicopathological variables individually, but not when adjusting for ER determined by Allred status. Only data from the derivation cohort (NSABP B-20) were available for LNO patients and this may have biased the results. The RSPC algorithm (*oncotype* DX plus age, tumour size and grade) showed a non-significant interaction test between chemotherapy benefit and RSPC risk group, and also used the NSABP B-20 data set. Three observational cohort studies were at high risk of confounding; one reported a statistically significant interaction test but this was only adjusted for limited factors. If predictive ability was assumed, it is unclear below which exact cut-off point patients could avoid chemotherapy (although one study suggests that this is a recurrence score of 20), as chemotherapy benefit is uncertain in the intermediate-risk group. Although TAILORx<sup>22</sup> (an ongoing RCT comparing long-term outcomes in patients treated with usual care vs. patients treated with usual care in conjunction with *oncotype* DX) will address the issue of whether or not low- and intermediate-risk patients can avoid chemotherapy, it is unclear to what extent it will address the question of whether or not the test can predict chemotherapy benefit. Considering the limitations of the available data, the EAG concludes that there remains uncertainty surrounding whether or not *oncotype* DX is associated with a predictive benefit of chemotherapy (i.e. a difference in relative effect by genomic risk group) and, if so, that there is uncertainty in the likely magnitude of this predictive effect within the clinical subgroups considered in this appraisal.

The TAILORx study<sup>22</sup> reported during the course of the assessment, and included some data relating to chemotherapy benefit prediction. The EAG prepared a preliminary appraisal of this evidence, which can be accessed via the NICE website.<sup>72</sup>

## Clinical utility: *oncotype* DX

In this review, clinical utility relates to the impact of the prospective use of the test on patient outcomes such as survival and recurrence. The ideal study design would be a RCT in which patients are randomised to treatment guided by the test or treatment in accordance with usual practice. Observational studies (either prospective or retrospective) in which patients received the test prospectively in clinical practice are at a higher risk of bias from confounding. Such studies cannot address the question of whether or not the test can improve patient outcomes relative to usual practice. They can, however, reveal something about the ability of the test to identify a group of patients at very low ROR who could avoid chemotherapy. Data relating to risk in intermediate- and high-risk categories are, without a no-test comparator arm, difficult to interpret in the context of clinical utility. Therefore, we have focused on outcome data in low-risk patients

and the use of chemotherapy in all groups. A full narrative synthesis of results can be found in *Report Supplementary Material 4*.

### Study and patient characteristics

Five data sets reported across nine publications<sup>22,65,66,68,69,73–75</sup> and one AiC manuscript were included. Study characteristics are presented in *Report Supplementary Material 4*. Two studies had a prospective trial design (within RCTs),<sup>22,73,74</sup> and the remainder were retrospective analyses of observational data. One further study, the SEER registry,<sup>67,68</sup> did not meet the inclusion criteria for the review in that only survival outcomes with < 5 years follow-up were reported, but it reported useful data on certain subgroups of interest to the review (micrometastases and race) and is presented here due to the paucity of other data relating to these characteristics.

Only one study (TAILORx)<sup>22</sup> randomised patients (HR+, HER2– and LN0) to treatment guided by the test or treatment in accordance with usual practice. Women with recurrence scores of < 11 were assigned to endocrine therapy only, whereas women with recurrence scores of 11–25 were randomised to either endocrine therapy plus chemotherapy or endocrine therapy only. As of July 2017, this study had only reported results for the low-risk (recurrence score of < 11) group ( $n = 1626$ ). Data for this group are effectively prospective observational data. The study reported in full in June 2018<sup>76</sup> and the EAG prepared a preliminary appraisal of this evidence, which can be accessed via the NICE website.<sup>72</sup>

The West German Study Group (WSG) PlanB<sup>73,74,77</sup> trial ( $n = 3198$ ) is also a prospective RCT, but does not aim to assess the clinical utility of onco $type$  DX, as it randomises clinically high-risk patients {pathological tumour stage (pT)1–T4c; LN+, or LN0 with a risk factor [ $\geq$  pT2, grade 2/3, high urokinase plasminogen activator (uPA)/plasminogen activator inhibitor-1 (PAI-1), aged < 35 years or HR-negative]} with 0–3 positive lymph nodes with a recurrence score of  $\geq 12$  to two different sorts of chemotherapy. However, a translational research aim was to assess the ROR in patients with recurrence scores of < 12 who were not treated with adjuvant chemotherapy. This group is, again, effectively a prospective observational cohort.

There were three retrospective cohorts in which patients were treated using onco $type$  DX,<sup>65,66,69,75</sup> and one further retrospective cohort that did not meet the inclusion criteria for the review.<sup>67,70</sup> The total number of patients included in these retrospective analyses is  $\approx 54,000$  (some double-counting from the Clalit Health Services cohort).<sup>66,69</sup> Patients were ER+, HER2– and must have had an onco $type$  DX test (it was unclear how patients were selected for testing, and this may have introduced spectrum bias). Two studies recruited only LN0 to lymph node micrometastases (LNmicro) patients,<sup>65,75</sup> and one reported LN0–LNmicro<sup>69</sup> and patients with micro metastases or between one and three lymph node metastases (LNmicro–LN3).<sup>66,69</sup> The study that did not meet the inclusion criteria recruited patients with LN0–3, and is included as it subgrouped patients in accordance with age (40–85 years), lymph node status (LN0, LNmicro–LN3, LNmicro only) and race (black, white, other).<sup>67,70</sup>

### Quality assessment

The highest level of evidence for clinical utility is a RCT of treatment guided by the test versus treatment guided in accordance with usual practice. Assessment with the Cochrane risk-of-bias tool for RCTs indicates that all studies are of too poor quality to meet this aim.

### Results: onco $type$ DX clinical utility

Data relating to the clinical utility of onco $type$  DX are presented in *Table 8*. A more detailed narrative synthesis is provided in *Report Supplementary Material 4*. All studies report data relating to recurrence or survival, but differences in cut-off points (recurrence score of < 11, < 12 and < 18), patient populations (clinically high risk, LN0 or LN+), treatment regimens (some patients had chemotherapy in some studies) and outcome measures (DRFS, DFS, DRFI, BCSS and OS) precluded a meaningful meta-analysis.

Across the studies in which chemotherapy was delivered in accordance with usual practice using onco $type$  DX, chemotherapy rates in patients at low risk (recurrence score of < 18) ranged from 1%<sup>69</sup> to

TABLE 8 Clinical utility results: oncotype DX

Study, first author and year	Study design	Patients	Subgroup	Treatment	Outcome (5 years)	Cut-off point <sup>a</sup>	Risk group, % risk of outcome (95% CI)			Comparison	Adjusted HR (95% CI) <sup>b</sup>
							Low	Intermediate	High		
<b>DRFS/DRFI/DFS</b>											
<i>LN0, cut-off point RS 18–30</i>											
Clalit Health Services, Stemmer 2016 <sup>69</sup>	R	ER+, HER2-, had oncotype DX test	LN0–1micro, n = 1594 <sup>69</sup>	<ul style="list-style-type: none"> <li>• RS &lt; 18: 1%</li> <li>• RS 18–30: 26%</li> <li>• RS &gt; 30: 89%</li> </ul>	DRFI	18–30	99.5 (98.4 to 99.8)	98.8 (97.2 to 99.4)	93.1 (87.1 to 96.3)		
MD Anderson, Le Du 2015 <sup>65</sup>	R	ER+, HER2-, stage 1, had oncotype DX test	LN0/LNmicro, n = 1030	Chemotherapy per group: <ul style="list-style-type: none"> <li>• RS &lt; 18: 6.4%</li> <li>• RS 18–30: 42.7%</li> <li>• RS &gt; 30: 89.8%</li> </ul>	DRFS	18–30	95.9 (93.0 to 97.6) <sup>c</sup>	NR	76.4 (59.2 to 87.1) <sup>c</sup>	p < 0.0001	<ul style="list-style-type: none"> <li>• High vs. low: 2.20 (0.90 to 5.36); p = 0.083</li> <li>• Intermediate vs. low: 1.88 (0.96 to 3.68); p = 0.066</li> <li>• High vs. intermediate: 1.17 (0.54 to 2.51); p = 0.690</li> </ul>
Memorial Sloan Kettering, Wen 2017 <sup>75</sup>	R	ER+, HER2-, stage 1 and 2, had oncotype DX test, low RS	LN0 or LNmicro, n = 1406	Chemotherapy: <ul style="list-style-type: none"> <li>• RS &lt; 18: 12%</li> </ul>	DRFI	< 18	99.6% <sup>d</sup>				
<i>LN0, cut-off point RS 11 (or 12)–25</i>											
Memorial Sloan Kettering, Wen 2017 <sup>75</sup>	R	ER+, HER2-, stage 1 and 2, had oncotype DX test, low RS	LN0 or LNmicro, n = 1406	Chemotherapy: <ul style="list-style-type: none"> <li>• RS &lt; 18: 12%</li> </ul>	DRFI	< 11	99.9% <sup>d</sup>				
TAILORx, Sparano 2015 <sup>22</sup>	P	HR+, HER2-, tumour size <sup>e</sup>	LN0, n = 1626	100% endocrine therapy	DRFS	< 11	99.3 (98.7 to 99.6)				
					IDFS	< 11	93.8 (92.4 to 94.9)				
<i>LN+, cut-off point RS 18–30</i>											
Clalit Health Services, Stemmer 2016 <sup>66</sup>	R	ER+, HER2-, had oncotype DX test	LN1micro–LN3, n = 627 <sup>66</sup>	Chemotherapy per group: <ul style="list-style-type: none"> <li>• RS &lt; 18: 7%</li> <li>• RS 18–30: 40%</li> <li>• RS &gt; 30: 90%</li> </ul>	DRFI	18–30	96.8 (NR)	93.4 (NR)	83.6 (NR)		
			LN1micro, n = 270 <sup>66</sup>		DRFI		99.3 (NR)	89.2 (NR)	80.6 (NR)		

continued

TABLE 8 Clinical utility results: oncotype DX (continued)

Study, first author and year	Study design	Patients	Subgroup	Treatment	Outcome (5 years)	Cut-off point <sup>a</sup>	Risk group, % risk of outcome (95% CI)			Comparison	Adjusted HR (95% CI) <sup>b</sup>	
							Low	Intermediate	High			
<i>LN+, cut-off point RS 11–25</i>												
Clalit Health Services, Stemmer 2016 <sup>66</sup>	R	ER+, HER2–, had oncotype DX test	LN1micro–LN3, n = 627 <sup>66</sup>	<ul style="list-style-type: none"> <li>● RS &lt; 11: 7%</li> <li>● RS 11–25: 18%</li> <li>● RS &gt; 25: 81%</li> </ul>	DRFI	11–25	95.1 (NR)	96.1 (NR)	86.8 (NR)			
			LN1micro, n = 270 <sup>66</sup>				97.8 (NR)	95.9 (NR)	83.9 (NR)			
<i>LN+/LNO, cut-off point RS 12–25</i>												
WSG PlanB, Nitz 2017 <sup>73,74,77</sup>	P	Clinically high-risk, <sup>g</sup> HR+, HER2– patients	LN0–3, <sup>73</sup> n = 2642	<ul style="list-style-type: none"> <li>● RS &lt; 12 endocrine therapy only;</li> <li>● RS ≥ 12, chemotherapy plus endocrine therapy</li> </ul>	IDFS	12–25	94.2 (91.2 to 97.3) <sup>h,i</sup>	94.3 (92.8 to 95.8) <sup>h</sup>	84.2 (80.6 to 87.8) <sup>h</sup>	HR = 2.33 (1.73 to 3.14); p < 0.001 <sup>l</sup>	For continuous score (100–75th vs. 0–25th percentiles): 1.73 (1.21 to 2.47); p = 0.001	
<b>BCSS and OS</b>												
<i>LNO, cut-off point RS 18–30</i>												
Clalit Health Services, Stemmer 2016 <sup>69</sup>	R	ER+, HER2–, had oncotype DX test	LN0–1micro, n = 1594 <sup>69</sup>	<ul style="list-style-type: none"> <li>● RS &lt; 18: 1%</li> <li>● RS 18–30: 26%</li> <li>● RS &gt; 30: 89%</li> </ul>	BCSS	18–30	99.9 (99.0 to 100.0)	98.5 (97.1 to 99.2)	90.6 (84.5 to 94.4)			
SEER registry, Petkov 2016, <sup>70</sup> Roberts 2016 <sup>67</sup>	R	HR+, HER2– <sup>k</sup>	LN0, 40–84 years of age, n = 38,568	<ul style="list-style-type: none"> <li>● RS &lt; 18: 7%</li> <li>● RS 18–30: 34%</li> <li>● RS &gt; 25: 69%</li> </ul>	LN0, 40–85 years:	BCSS < 5 years	18–30	99.6 (99.4 to 99.7)	98.6 (98.3 to 98.9)	95.6 (94.4 to 96.6)	<ul style="list-style-type: none"> <li>● Intermediate vs. low: HR 3.1 (2.3 to 4.3)</li> <li>● High vs. low: HR 11.0 (7.8 to 15.5)</li> <li>● All: p &lt; 0.001</li> </ul>	<ul style="list-style-type: none"> <li>● Intermediate vs. low: HR 3.0 (2.1 to 4.2)</li> <li>● High vs. low: HR 7.8 (5.3 to 11.6)</li> <li>● All: p &lt; 0.001</li> </ul>
			LN0, black, n = 2890		BCSS < 5 years	18–30	99.2 (0.28)	98.2 (0.58)	94.3 (2.17)	p < 0.0001		
			LN0, white, n = 33,684		BCSS < 5 years	18–30	99.6 (0.07)	98.6 (0.15)	95.6 (0.61)	p < 0.0001		
			LN0, other race, n = 3321		BCSS < 5 years	18–30	99.8 (0.15)	99.2 (0.36)	95.3 (1.89)	p < 0.0001		
<i>LNO, cut-off point RS 11–25</i>												
SEER registry, Petkov 2016, <sup>70</sup> Roberts 2016 <sup>67</sup>	R	HR+, HER2– <sup>k</sup>	LN0, all ages, n = 40,134		Chemotherapy per group: NR	BCSS < 5 years	11–25	99.6 (99.4 to 99.8)	99.3 (99.2 to 99.4)	96.4 (95.6 to 97.0)	p < 0.001	
TAILORx, Sparano 2015 <sup>22</sup>	P (RCT)	HR+, HER2–, tumour size, <sup>a</sup> n = 1629	LN0		100% endocrine therapy	OS	< 11	98.0 (97.1 to 98.6)	N/A	N/A	N/A	

Study, first author and year	Study design	Patients	Subgroup	Treatment	Outcome (5 years)	Cut-off point <sup>a</sup>	Risk group, % risk of outcome (95% CI)			Comparison	Adjusted HR (95% CI) <sup>b</sup>
							Low	Intermediate	High		
<i>LN+, cut-off point RS 18–30</i>											
Clalit Health Services, Stemmer 2016 <sup>66</sup>	R	ER+, HER2-, had oncoprote DX test	LN1micro–LN3, n = 627 <sup>66</sup>	Chemotherapy per group:	BCSS	18–30	99.1 (NR)	97.4 (NR)	86.9 (NR)		
			LN1micro, n = 270 <sup>66</sup>	<ul style="list-style-type: none"> <li>● RS &lt; 18: 7%</li> <li>● RS 18–30: 40%</li> <li>● RS &gt; 30: 90%</li> </ul>	BCSS	18–30	99.3 (NR)	96.8 (NR)	83.9 (NR)		
SEER registry, Petkov 2016, <sup>70</sup> Roberts 2016 <sup>67</sup>	R	HR+, HER2- <sup>k</sup>	LNmicro–LN3, all ages, n = 4691	LN1–3:	BCSS < 5 years <sup>m,n</sup>	99.0 (98.0 to 99.5) <sup>118</sup>	97.7 (95.9 to 98.7)	85.7 (76.2 to 91.6)	p < 0.001		
			LN1–3, black, n = 328	<ul style="list-style-type: none"> <li>● &lt; 18: 23%</li> <li>● 18–30: 47%</li> <li>● &gt; 25: 75%</li> </ul>	BCSS < 5 years <sup>m,n</sup>	18–30	99.4 (0.56)	98.9 (1.12)	91.3 (8.31)	p = 0.4117	
			LN1–3, white, n = 4,021		BCSS < 5 years <sup>m,n</sup>	18–30	99.0 (0.39)	97.6 (0.75)	84.1 (4.21)	p < 0.0001	
			LN1–3, other race, n = 320		BCSS < 5 years <sup>m,n</sup>	18–30	98.5 (1.53)	99.1 (0.92)	100 (0)	p = 0.8427	
			LNmicro, n = 2820 <sup>68</sup>	NR	BCSS < 5 years <sup>m,n</sup>		98.9 (97.4 to 99.6)	99.1 (97.9 to 99.6)	84 (74.1 to 90.4)		
<i>LN+, cut-off point RS 11–25</i>											
Clalit Health Services, Stemmer 2016 <sup>66</sup>	R	ER+, HER2-, had oncoprote DX test	LN1micro–LN3, n = 627 <sup>66</sup>	<ul style="list-style-type: none"> <li>● RS &lt; 11: 7%</li> <li>● RS 11–25: 18%</li> <li>● RS &gt; 25: 81%</li> </ul>	BCSS	11–25	98.0 (NR)	99.0 (NR)	90.4 (NR)		
			LN1micro, n = 270 <sup>66</sup>		BCSS		97.8 (NR)	98.8 (NR)	89.3 (NR)		
SEER registry, Petkov 2016, <sup>70</sup> Roberts 2016 <sup>67</sup>	R	HR+, HER2- <sup>k</sup>	LNmicro–LN3, all ages, n = 4691	LN1–3:	BCSS < 5 years <sup>m,n</sup>	11–25	99.0 (98.0 to 99.5) <sup>118</sup>	97.7 (95.9 to 98.7)	85.7 (76.2 to 91.6)	p < 0.001	
				<ul style="list-style-type: none"> <li>● &lt; 18: 23%</li> <li>● 18–30: 47%</li> <li>● &gt; 25: 75%</li> </ul>							

BCD, breast cancer death; FFR, freedom from recurrence of breast cancer; K–M, Kaplan–Meier; N/A, not applicable; NR, not reported; P, prospective; R, retrospective; RS, oncoprote DX recurrence score.

a Range of intermediate group (e.g. where cut-off points were < 18, 18–30 and > 30 for low, intermediate or high, respectively, this is shown as 18–30).

b Adjustments: Le Du 2015: not reported; Stemmer: age, tumour size, grade; Nitz 2017: nodal status, tumour size, grade, ER, PR, Ki-67, IHC4; SEER registry: age, grade, tumour size, race.

c Median follow-up 58 months.

d Median follow-up 46 months.

e Tumour size 1.1–5 cm or 0.6–1.0 cm in intermediate- or high-risk tumours.

f Overall survival data not presented here as follow-up was < 5 years. Nitz *et al.* 2017<sup>77</sup> published after searches, but only added 95% CIs to data already available from conference abstracts.

g HER2-; pT1–T4c; LN+ (or LNO with a risk factor (CpT2, grade 2/3, high uPAVPAI-1, < 35 years, or HR-negative)).

h 55-month follow-up.<sup>73</sup>

i These data for 348/404 patients with RS of < 12, in whom chemotherapy was omitted after a protocol amendment.

j Assume low risk vs. intermediate/high risk.

k HR+ by oncoprote DX and by IHC; HER2 status by oncoprote DX.

l 98.7% (95% CI 97.1% to 99.4%) for LN1–3.

m Clinical advice to the EAG stated that for survival outcomes, a minimum of 5-year data were required. These data are presented as an exception as they are included in Genomic Health's submission, and it presents data on micrometastases and by number of lymph nodes, and analyses relating to race.

n Follow-up 38 months.

12%<sup>75</sup> (four studies<sup>65,67,69,70,75</sup>) in LN0 patients and from 7% to 23% (two studies<sup>66,67,70</sup>) in LN+ patients. In intermediate-risk (recurrence score of 18–30) patients, chemotherapy rates ranged from 26%<sup>69</sup> to 43%<sup>65</sup> (three studies<sup>65,69,75</sup>) in LN0 patients and from 40%<sup>66</sup> to 47%<sup>67,70</sup> (two studies<sup>66,67,69</sup>) in LN+ patients. These data perhaps indicate that lymph node status was considered in treatment decisions, although no formal comparison has been made. In high-risk patients, chemotherapy rates were similar in LN0 (90%<sup>65</sup> and 89%<sup>69</sup>) and LN+ patients (90%).<sup>66</sup>

Studies generally reported different outcomes [5-year DRFS ( $n = 2$ ),<sup>22,65</sup> DRFI ( $n = 2$ ),<sup>66,69,75</sup> IDFS ( $n = 2$ ),<sup>22,73,74,77</sup> BCSS ( $n = 3$ )<sup>66,67,69,70</sup> and OS ( $n = 1$ )<sup>22</sup>], making comparisons across studies difficult. For outcomes including recurrence (DRFS, DRFI and IDFS), low-risk patients with recurrence scores of  $< 18$ <sup>65,66,69,75</sup> had outcomes ranging from 95.9%<sup>65</sup> (5-year DRFI) to 99.6%<sup>75</sup> (5-year DRFI) in LN0 patients ( $n = 3$ ) and 97%<sup>66</sup> (5-year DRFI) in LN+ patients, whereas low-risk patients with recurrence scores of  $< 11$  had outcomes of 94%<sup>22</sup> (5-year IDFS) and 99.9%<sup>75</sup> (5-year DRFI) in LN0 ( $n = 2$ )<sup>22,75</sup> and 95%<sup>66</sup> (5-year DRFI) in LN+ patients ( $n = 1$ ).<sup>66</sup> Clinical advice to the EAG suggests that these levels of recurrence are acceptable in a low-risk population.

It was beyond the scope of the assessment to determine whether the newer cut-off points (of 11–25) should be used, or whether the original cut-off points of recurrence score 18–30 would be preferable. Data relating to this are summarised in the narrative synthesis (see *Report Supplementary Material 4*) and *Table 8*, and the general observation can be made that although use of lower cut-off points may result in better outcomes in the low-risk group (although data are mixed on this point), it would also result in fewer patients being classified as low risk.

Data relating to intermediate- and high-risk patients are included in the narrative synthesis (see *Report Supplementary Material 4*) and appear in *Table 8*. It was not possible to draw any conclusions regarding whether or not patients in intermediate- and high-risk categories had better outcomes as a result of using oncotype DX to guide treatment, as there were no comparator (no-oncotype DX) groups.

The data on micrometastases are difficult to interpret as there is no analysis that reports all nodal statuses in the same patient group (i.e. LN0, LNmicro, LN1–3). The analyses that have been done show that the trend for worse outcomes with increasing risk group holds true in patients with micrometastases.<sup>66,67</sup>

The data relating to the performance of the test in patients of different races showed that BCSS survival differed similarly in accordance with risk categories in all race categories.<sup>67</sup>

## Conclusions

Without the highest level of evidence, it is not possible to conclude whether or not patient outcomes would be affected by use of the test in a clinical setting. In LN0 patients, use of the test in clinical practice appears to result in low rates of chemotherapy use in low-risk patients (1–12%), with acceptable outcomes (DRFS/DRFI/IDFS 96–99.6%). Rates of chemotherapy use increased with increasing risk category, and were generally higher in LN+ patients; only one study reported DRFS/DRFI/IDFS for LN+ patients, which was 97% (7% received chemotherapy). It was not possible to draw any conclusions regarding whether or not patients in intermediate- and high-risk categories had better outcomes as a result of using oncotype DX owing to the observational nature of the studies.

## Results: MammaPrint

### Development: MammaPrint

A description of the development of MammaPrint is provided in *Report Supplementary Material 5*.

### Prognostic performance: MammaPrint

Here we summarise some key findings relating to DRFS/DRFI. See *Report Supplementary Material 5* for a full narrative synthesis and data relating to survival outcomes.

## Study characteristics

Several publications describe validation of the prognostic value of MammaPrint. Many include overlapping cohorts of patients, sometimes pooled with other cohorts, sometimes focusing on patient subgroups (e.g. ER+ or LN0/LN+), sometimes updating the data with longer follow-up and reporting a range of different outcomes. Therefore, it should be noted that there is some overlap between patient cohorts within the references included here. *Table 9* shows both the study reference(s) (column 1) and the cohort(s) (column 2) used for each analysis, and *Report Supplementary Material 5* describes the cohorts in more detail.

There were nine main cohorts, which were small, retrospective analyses of consecutive patient series: four were from the Netherlands,<sup>79,80,84,87,89</sup> two were multi-European,<sup>85,88</sup> two were from the USA<sup>90,96</sup> and one was from Japan<sup>95</sup> (total  $n = 1805$ ). They covered a mix of LN0 and LN+ patients, with variable proportions receiving endocrine therapy and chemotherapy. In most studies, around 70–80% were ER+, and *HER2* status was not well reported. Four analyses pooling some of the above cohorts<sup>78,83,87,93</sup> are also included due to their focus on specific subgroups. In addition, there was one reanalysis of a RCT [the Swedish Stockholm Tamoxifen-3 (STO-3) trial;  $n = 538$ ], of which a subgroup had endocrine monotherapy.<sup>78,91,92,94,97</sup>

## Quality assessment

One study (van de Vijver *et al.*<sup>79</sup>) included a small proportion of patients from the derivation cohort, and may therefore overestimate prognostic performance, although a 'leave-one-out' analysis was used to mitigate this problem to some extent. Most analyses excluded some patients from the original cohort, some because of insufficient tumour sample, which may introduce bias due to attrition of patients with smaller tumours. Blinding of test assessors to outcomes was reported in around half of the studies. Outcomes did not always match standardised definitions and it was not always possible to tell from the publication whether or not all deaths and breast cancer deaths were counted as events or were censored. Different levels of treatment use in the high- and low-risk groups may confound results by reducing separation between the groups in recurrence rates, and selection of patients in accordance with treatment may introduce spectrum bias because these patients may be systematically different from the whole population. Many studies included a proportion of patients who were not in the scope of this research.

## Distribution of patients by risk group

The percentage of patients categorised as low risk ranged from 20% to 71% and the percentage of those categorised as high risk ranged from 29% to 80% across seven analyses of LN0 patients.<sup>84,86,88,89,91,95,96</sup> In two analyses of LN+ patients,<sup>85,89</sup> the percentages categorised as low risk were 38% and 41%, whereas the percentages categorised as high risk were 59% and 62%.

## Prognostic performance: unadjusted analyses

Prognostic data for MammaPrint is provided in *Tables 10* and *11*. Among LN0/LN+ studies, Mook *et al.*<sup>87</sup> pooled 964 patients from seven series<sup>79–81,84–86,88</sup> (one-third had endocrine therapy and one-quarter had chemotherapy) and showed that MammaPrint was statistically significantly prognostic for 10-year DRFS (HR 2.70, 95% CI 1.88 to 3.88;  $p < 0.0001$ ), with 10-year DRFS of 87% in low-risk patients.<sup>87</sup> Knauer *et al.*<sup>83</sup> pooled 541 patients (restricted to LN0–3 patients, 100% endocrine therapy, 42% chemotherapy) from six of these series, and also reported statistically significant results. In terms of longer follow-up of the original van de Vijver *et al.*<sup>79</sup> cohort (51% LN0, 37% had chemotherapy and 14% had endocrine therapy), MammaPrint was statistically significantly prognostic in an unadjusted analysis of DRFS over 0–25 years<sup>89</sup> in a LN0/LN+ cohort;<sup>79</sup> most of this difference was in the first 5 years (HR 9.6, 95% CI 4.2 to 22.1). A separate US series (Yao *et al.*;<sup>90</sup> 72% LN0, 43% had chemotherapy and 87% had endocrine therapy) also showed statistically significant prognostic ability for DRFS at 10 years (HR 2.91, 95% CI 0.97 to 8.68;  $p = 0.045$ ) (see *Table 9*) with DRFS rates in the low-risk group of 96% at 10 years; results were similar (low-risk 10-year DRFS 98%) in a subset with no chemotherapy.

Among LN0 patients, in the only reanalysis of a RCT the STO-3 trial (van 't Veer *et al.*<sup>91</sup>) reported 10-year DRFS rates (93% in low-risk patients, 85% in high-risk patients) (see *Table 9*) but no statistically significant levels were reported.<sup>91</sup> Four out of five retrospective LN0 cohorts reported statistically significant prognostic

**TABLE 9** Prognostic performance of MammaPrint: DRFS/DRFI

Reference (first author and year)	Cohorts	Population	Nodal status	ET/chemotherapy	Test or comparator	Percentage of patients per group		Percentage DRFS/DRFI risk: 0–5 years		Percentage DRFS/DRFI risk: 0–10 years		DRFS/DRFI: HR (95% CI)
						Low	High	Low	High	Low	High	
<b>Pooled analyses of patient cohorts: LN status mixed</b>												
<i>Variable ET and chemotherapy</i>												
Beumer 2016, <sup>78</sup> n = 217	Lobular cancers, five pooled series <sup>79–82</sup>	94% ER+, 92% HER2–	LN0, 66% LN+, 34%	59% ET, 22% chemotherapy	MammaPrint	76	24	NR	NR	NR	NR	0–10 years: 3.31 (1.79 to 6.12); p < 0.001
	Lobular cancer	93% ER+, 93% HER2–	LN0	51% ET, 12% chemotherapy	MammaPrint	82	18	NR	NR	NR	NR	0–10 years: 7.81 (2.89 to 21.07); p < 0.001
Knauer 2010, <sup>83</sup> n = 541	Pooled six series <sup>79–81,84–86</sup>	90% ER+, 89% HER2–	LN0, 49% LN1–3, 51%	All ET, 42% chemotherapy	MammaPrint	47	53	95	82	NR	NR	0–5 years: 3.88 (1.99 to 7.58); p < 0.01
Mook 2010, <sup>87</sup> n = 964	Pooled seven series <sup>79–81,84–86,88</sup> T1 only	84% ER+, 68% HER2–	LN0, 72% LN+, 27%	32% ET, 22% chemotherapy	MammaPrint	54	46	95	80	87	72	0–10 years: 2.70 (1.88 to 3.88); p < 0.001
		n = 552		No ET, no chemotherapy	MammaPrint			96	78	86	70	0–10 years: 2.90 (1.83 to 4.79); p < 0.001
<b>Retrospective studies: LN status mixed</b>												
<i>Variable ET and chemotherapy</i>												
Drukker 2014, <sup>89</sup> n = 295	van de Vijver 2002 <sup>79</sup>	77% ER+ HER2 NR	LN0, 51%, LN1–3, 36%, LN > 3, 13%	14% ET, 37% chemotherapy	MammaPrint	39	61	94.7	58.5	82.0	50.0	0–5 years: 9.6 (4.2 to 22.1); p = NR 5–10 years: 1.1 (0.5 to 2.5); p = NR 10–15 years: 1.2 (0.2 to 6.0); p = NR 15–20 years: 1.1 (0.1 to 17.9); p = NR 20–25 years: 0.3 (0 to 2.9); p = NR 0–25 years: 3.1 (2.02 to 4.86); p < 0.0001

Reference (first author and year)	Cohorts	Population	Nodal status	ET/chemotherapy	Test or comparator	Percentage of patients per group		Percentage DRFS/DRFI risk: 0–5 years		Percentage DRFS/DRFI risk: 0–10 years		DRFS/DRFI: HR (95% CI)
						Low	High	Low	High	Low	High	
Yao 2015, <sup>90</sup> <i>n</i> = 238	NorthShore & Fox Chase, USA	All HR+	LN0, 72%, LN+, 28%	87% ET, 43% chemotherapy	MammaPrint	60	40	NR	NR	96	87	0–10 years: 2.91 (0.97 to 8.68); <i>p</i> = 0.045
		All HER2– HR+/HR–	LN+/LN0	No chemotherapy	MammaPrint	61	39	NR	NR	98	85	NR
<b>Reanalyses of RCTs: LN0</b>												
<i>100% ET monotherapy</i>												
van 't Veer 2017, <sup>91</sup> Esserman <sup>92</sup>	STO-3 trial: ER+ analysis	All ER+  HER2 NR	LN0	All ET, no chemotherapy	MammaPrint	71	29	NR	NR	93	85	NR
ET: <i>n</i> = 281												
<i>No ET and chemotherapy</i>												
van 't Veer 2017, <sup>91</sup> Esserman <sup>92</sup>	STO-3 trial: ER+ analysis	All ER+  HER2 NR	LN0	No ET, no chemotherapy	MammaPrint	67	33	NR	NR	83	70	NR
No ET: <i>n</i> = 257												
<b>Pooled analyses of patient cohorts: LN0</b>												
<i>No ET and chemotherapy</i>												
Bueno-de- Mesquita 2011 <sup>93</sup>	Pooled <sup>79,84</sup>  <i>n</i> = 186	76% ER+  76% HER2–	LN0	No ET/ chemotherapy	MammaPrint	45	55	NR	NR	88	55	NR
<b>Retrospective studies: LN0</b>												
<i>Variable ET and chemotherapy</i>												
Bueno-de- Mesquita 2009, <sup>84</sup> <i>n</i> = 123	Bueno-de-Mesquita 2009 <sup>84</sup>	76% ER+  93% HER2–	LN0	22% ET, 25% chemotherapy	MammaPrint	52	48	98	78	NR	NR	0–5 years: 5.7 (1.6 to 20); <i>p</i> = 0.007
					AOL	NR	NR	NR	NR	NR	NR	0–5 years: 4.6 (0.61 to 35.1); <i>p</i> = 0.14
					NPI	NR	NR	NR	NR	NR	NR	0–5 years: 2.2 (0.78 to 6.5); <i>p</i> = 0.14
Buyse 2006 <sup>88</sup>	TRANSBIG <sup>88</sup>	70% ER+	LN0	No ET/ chemotherapy	MammaPrint	37	63	NR	NR	90	71	DRFI all follow-up (median 13.6 years)
Company submission <sup>94</sup>	<i>n</i> = 302	HER2 NR										2.32 (1.35 to 4.00); <i>p</i> = 0.002
					AOL							1.68 (0.92 to 3.07); <i>p</i> = 0.092
					NPI							1.65 (1.02 to 2.66); <i>p</i> = 0.043

continued

**TABLE 9** Prognostic performance of MammaPrint: DRFS/DRFI (continued)

Reference (first author and year)	Cohorts	Population	Nodal status	ET/chemotherapy	Test or comparator	Percentage of patients per group		Percentage DRFS/DRFI risk: 0–5 years		Percentage DRFS/DRFI risk: 0–10 years		DRFS/DRFI: HR (95% CI)
						Low	High	Low	High	Low	High	
Drukker 2014, <sup>89</sup> Bueno-de-Mesquita 2009, <sup>84</sup> n = 151	van de Vijver 2002 <sup>79</sup>	72% ER+  HER2 NR	LN0	4% ET, 4% chemotherapy	MammaPrint	40	60	94.9 <sup>89</sup>	52.4 <sup>89</sup>	86 <sup>84</sup>	50 <sup>84</sup>	0–10 years: 5.5 (2.5 to 12); p < 0.001 <sup>84</sup>  0–25 years: 4.57 (2.31 to 9.04); p < 0.0001 <sup>89</sup>
					AOL	NR	NR	NR	NR	NR	NR	0–10 years: 1.7 (0.84 to 3.6); p = 0.14
					NPI	NR	NR	NR	NR	NR	NR	0–10 years: 3.1 (1.6 to 5.9); p < 0.001
Ishitobi 2010, <sup>95</sup> n = 102	Osaka Medical Centre	51% ER+  HER2 NR	LN0	73% ET, 28% chemotherapy	MammaPrint	20	80	100	94	NR	NR	NR
Mook 2010, <sup>86</sup> n = 148	NKI 1984–96 <sup>86</sup> (55–71 years)	78% ER+  HER2 NR	LN0	18% ET, no chemotherapy	MammaPrint	61	39	93	72	80	67	0–5 years: 4.6 (1.8 to 12.0); p = 0.001  0–10 years: data per group, but p-values NR
Wittner 2008, <sup>96</sup> n = 100	Massachusetts, USA	80% ER+  HER2 NR	LN0	24% ET, 21% chemotherapy	MammaPrint	27	73	NR	NR	NR	NR	DRFI:  ● 0–5 years: PPV = 12%, NPV = 100%; p = 0.192 ● 0–10 years: PPV = 14%, NPV = 100%; p = 0.330
<b>Retrospective studies: LN+</b>												
Variable ET and chemotherapy												
Drukker 2014, <sup>89</sup> n = 144	van de Vijver 2002 <sup>79</sup>	ER+/ER–, HER2 NR	LN1–3, 74%, LN > 3, 26%	Some ET, some chemotherapy	MammaPrint	38	62	94.5	64.7	78.6	54.3	0–25 years: 2.24 (1.25 to 4.00); p = 0.01
Mook 2009, <sup>85</sup> n = 241	NKI and Italy <sup>85</sup>	79% ER+, 84% HER2–	LN1–3	73% ET, 56% chemotherapy	MammaPrint	41	59	98	80	91	76	0–10 years: 4.13 (1.72 to 9.96); p = 0.002
ET, endocrine therapy; NKI, Netherlands Cancer Institute; NPV, negative predictive value; NR, not reported; PPV, positive predictive value; TRANSBIG, Translating molecular knowledge into early breast cancer management: building on the BIG (Breast International Group) network for improved treatment tailoring.												

**TABLE 10** Prognostic performance of MammaPrint for patients at high or low clinical risk

Reference (first author and year)	Cohorts	Population	Nodal status	ET/chemotherapy	Outcome	Test or comparator	Percentage of patients per group		Percentage risk of outcomes: 0–5 years		Percentage risk of outcomes: 0–10 years		HR (95% CI)
							Low	High	Low	High	Low	High	
<b>Low risk via AOL + NPI + St Gallen criteria (LN0)</b>													
Bueno-de-Mesquita 2011 <sup>93</sup>	Pooled, <sup>79,84</sup> <i>n</i> = 139	ER+, low clinical risk	LN0	No ET/chemotherapy	DRFI	MammaPrint	77	23	NR	NR	87	70	0–10 years: HR NR; <i>p</i> = 0.19
					OS	MammaPrint	77	23	NR	NR	100	86	0–10 years: HR NR; <i>p</i> = 0.016
<b>Discordant risk via AOL + NPI + St Gallen criteria (LN0)</b>													
Bueno-de-Mesquita 2011 <sup>93</sup>	Pooled, <sup>79,84</sup> <i>n</i> = 139	ER+, discordant clinical risk	LN0	No ET/chemotherapy	DRFI	MammaPrint	66	34	NR	NR	91	63	0–10 years: HR NR; <i>p</i> = 0.004
					OS	MammaPrint	66	34	NR	NR	88	58	0–10 years: HR NR; <i>p</i> = 0.06
<b>High risk via AOL + NPI + St Gallen criteria (LN0)</b>													
Bueno-de-Mesquita 2011 <sup>93</sup>	Pooled, <sup>79,84</sup> <i>n</i> = 139	ER+, high clinical risk	LN0	No ET/chemotherapy	DRFI	MammaPrint	27	73	NR	NR	77	45	0–10 years: HR NR; <i>p</i> = 0.19
					OS	MammaPrint	27	73	NR	NR	77	53	0–10 years: HR NR; <i>p</i> = 0.17
<b>High risk via AOL (LN+)</b>													
Mook 2009 <sup>85</sup>	NKI plus Italy <sup>85</sup> <i>n</i> = 209	High-risk AOL	LN1–3	Some ET, some chemotherapy	BCSS	MammaPrint	NR	NR	NR	NR	94	76	0–10 years: 4.12 (1.45 to 11.76); <i>p</i> = 0.008

ET, endocrine therapy; NKI, Netherlands Cancer Institute; NR, not reported.

**TABLE 11** Additional prognostic value for DRFS/DRFI: MammaPrint

Reference (first author and year)	Cohorts	Population	Nodal status	ET/chemotherapy	Test or comparator <sup>3</sup>	C-index (AUC) (95% CI)	Increase in LR $\chi^2$ over clinicopathological factors <sup>a</sup>	Multivariable model adjuvant for clinicopathological factors, <sup>a</sup> AOL <sup>b</sup> or NPI: <sup>c</sup> HR (95% CI)
<b>Pooled analyses of patient cohorts: LN status mixed</b>								
<i>Variable ET and chemotherapy</i>								
Beumer 2016, <sup>78</sup> n = 217	Lobular cancers, five pooled series <sup>79-82</sup>	94% ER+, 92% HER2-	LN0, 66%; LN+, 34%	59% ET, 22% chemotherapy	MammaPrint			10 years: 2.08 (1.05 to 4.14); $p = 0.037^a$
Lobular cancer		93% ER+, 93% HER2-	LN0	51% ET, 12% chemotherapy	MammaPrint			10 years: 6.40 (2.14 to 19.17); $p = 0.001^a$
Mook 2010, <sup>87</sup> n = 941	Pooled seven series <sup>79-81,84-86,88</sup>	84% ER+, 68% HER2-	LN0, 72%; LN+, 27%	32% ET, 22% chemotherapy	MammaPrint			10 years: 2.43 (1.56 to 3.77); $p < 0.001^a$
		All ER+ (n = 788)	LN+/LN0	Some ET/ chemotherapy	MammaPrint			10 years: 2.51 (1.60 to 3.95); $p < 0.001^a$
		n = 552	LN+/LN0	No ET/ chemotherapy	MammaPrint			10 years: 2.54 (1.49 to 4.34); $p = 0.001^a$
<b>Retrospective studies: LN status mixed</b>								
<i>Variable ET and chemotherapy</i>								
van de Vijver, <sup>79</sup> n = 295	van de Vijver <sup>79</sup>	77% ER+, HER2 NR	LN0, 51%; LN+, 49%	14% ET, 37% chemotherapy	MammaPrint			10 years: 4.6 (2.3 to 9.2); $p < 0.001^a$
Yao 2015, <sup>90</sup> n = 373	NorthShore & Fox Chase	74% ER+, 83% HER2-	LN0, 72%; LN+, 28%	65% ET, 58% chemotherapy	MammaPrint			10 years: 3.01 (0.88 to 10.33); $p = 0.08^a$
<b>Pooled analyses of patient cohorts: LN0</b>								
<i>No ET and chemotherapy</i>								
Bueno-de-Mesquita 2011, <sup>93</sup> n = 186	Pooled <sup>79,84</sup>	76% ER+, 76% HER2-	LN0	No ET/ chemotherapy	MammaPrint		Change log-likelihood, $p < 0.001$	
<b>Retrospective studies: LN0</b>								
<i>Variable ET and chemotherapy</i>								
Bueno-de-Mesquita 2009, <sup>84</sup> n = 123	Bueno-de-Mesquita <sup>84</sup>	76% ER+, 93% HER2-	LN0	22% ET, 25% chemotherapy	MammaPrint	<ul style="list-style-type: none"> <li>Clinicopathological: 0.66 (0.50 to 0.82)</li> <li>Clinicopathological plus MammaPrint: 0.75 (0.61 to 0.89)</li> <li>MammaPrint: 0.69 (0.56 to 0.82)</li> </ul>	Change log-likelihood 5.5, $p = 0.023$	5 years: 4.8 (1.3 to 17); $p = 0.018^b$  5.4 (1.4 to 21); $p = 0.015^c$

Reference (first author and year)	Cohorts	Population	Nodal status	ET/chemotherapy	Test or comparator <sup>a</sup>	C-index (AUC) (95% CI)	Increase in LR $\chi^2$ over clinicopathological factors <sup>a</sup>	Multivariable model adjuvant for clinicopathological factors, <sup>a</sup> AOL <sup>b</sup> or NPI: <sup>c</sup> HR (95% CI)
van de Vijver 2002, <sup>79</sup> Bueno-de-Mesquita 2009, <sup>84</sup> Buyse 2006, <sup>88</sup> n = 151	van de Vijver <sup>79</sup>	72% ER+, HER2 NR	LN0	4% ET, 4% chemotherapy	MammaPrint	<ul style="list-style-type: none"> <li>Clinicopathological: 0.70 (0.61 to 0.79)</li> <li>Clinicopathological plus MammaPrint: 0.76 (0.68 to 0.85)</li> <li>MammaPrint: 0.68 (0.60 to 0.77)</li> </ul>	Change log-likelihood 15.8, $p < 0.01$	<ul style="list-style-type: none"> <li>10 years:<sup>84</sup> 5.3 (2.4 to 12); <math>p &lt; 0.001^b</math></li> <li>4.3 (1.8 to 10); <math>p = 0.001^c</math></li> <li>All follow-up (median 6.7 years):<sup>88</sup> 6.07 (2.64 to 13.98)<sup>b</sup></li> </ul>
<i>No ET and chemotherapy</i>								
Buyse 2006, <sup>88</sup> n = 302	TRANSBIG <sup>88</sup>	70% ER+, HER2 NR	LN0	No ET/ chemotherapy	MammaPrint			<ul style="list-style-type: none"> <li>5 years: 4.68 (CI NR)<sup>b</sup></li> <li>10 years: 3.5 (CI NR)<sup>b</sup></li> <li>All follow-up (median 13.6 years): 2.13 (1.19 to 3.82);<sup>b</sup> 2.15 (1.19 to 3.92)<sup>c</sup></li> </ul>
<b>Retrospective studies: LN+</b>								
<i>Variable ET and chemotherapy</i>								
Mook 2009, <sup>85</sup> n = 241	NKI plus Italy <sup>85</sup>	79% ER+, 84% HER2-	LN1-3	73% ET, 56% chemotherapy	MammaPrint			10 years: 2.99 (0.996 to 8.99); $p = 0.051^a$

ET, endocrine therapy; LR, likelihood ratio; NKI, Netherlands Cancer Institute; TRANSBIG, Translating molecular knowledge into early breast cancer management: building on the BIG (Breast International Group) network for improved treatment tailoring.

a Adjusted for:

- van de Vijver 2002<sup>79</sup> – age, lymph node status, tumour size, grade, vascular invasion, ER status, surgery type, chemotherapy and endocrine therapy.
- Mook 2009 (LN1-3) and Mook 2010 (pooled) – age, tumour size, nodal status, grade, ER, HER2, surgery, endocrine therapy, chemotherapy.
- Bueno-de-Mesquita 2011 and 2009 – age, tumour size, grade, ER, PR, HER2.
- Yao 2015 – age, tumour size, grade, ER, HER2.
- Beumer 2016 – age, nodal status, grade, ER, HER2, chemotherapy (similar results when only adjusting for clinicopathological factors associated with MammaPrint outcome).

b Adjusted for AOL.

c Adjusted for NPI.

performance of MammaPrint for DRFS/DRFI at varying time points, based on unadjusted HRs between risk groups.<sup>84,86,88,89</sup> The 10-year DRFS/DRFI rates in low-risk patients ranged from 80% to 90% across three analyses (with varying rates of endocrine therapy and chemotherapy use).<sup>84,86,88</sup>

Three of the LNO cohorts<sup>84,88,89</sup> included comparisons with AOL and NPI, which appeared to have less prognostic value than MammaPrint, although no statistical comparisons were reported. There were no comparisons with other risk tools such as Predict or Modified Adjuvant! Online (mAOL). Among LN+ patients, two cohorts reported statistically significant prognostic performance of MammaPrint based on unadjusted HRs between risk groups, with 10-year DRFS rates in low-risk patients of 79% and 91% (with varying rates of endocrine therapy and chemotherapy use).<sup>85,89</sup>

See *Report Supplementary Material 5* for subgroup analyses in patients with low or high clinical risk and in patients with lobular breast cancer, and for OS and BCSS outcomes.

### Additional prognostic value

Several studies reported adjusted analyses relating to the additional prognostic value of MammaPrint over existing clinicopathological risk scores and clinicopathological variables. A pooled analysis of LNO/LN+ patients from seven series<sup>79–81,84,85,87,88</sup> showed that MammaPrint was statistically significantly prognostic for 10-year DRFS in a multivariable analysis adjusting for clinicopathological variables. However, in the US series (Yao *et al.*<sup>90</sup>), MammaPrint was borderline non-statistically significant in a multivariable analysis ( $p = 0.08$ ). Among LNO patients, MammaPrint was statistically significantly prognostic for DRFI when adjusted for AOL or NPI in three cohorts reported across two publications.<sup>84,88</sup> C-indices from two<sup>79,84</sup> of these cohorts showed higher values when MammaPrint was included alongside clinicopathological factors than for either alone, although differences were not statistically compared.<sup>84</sup> In one analysis of LN+ patients, MammaPrint was borderline statistically significant for 10-year DRFS and statistically significantly prognostic for 10-year BCSS,<sup>85</sup> although in another analysis<sup>79</sup> BCSS at 10 years was borderline non-statistically significant.

### Conclusions: MammaPrint prognostic performance

The prognostic value of MammaPrint is based on nine retrospective analyses, four pooled analyses (including six of the nine retrospective series and one prospective series) and one reanalysis of a RCT. Studies were variable in terms of nodal status, ER status and receipt of endocrine therapy and chemotherapy. The percentage of LNO patients categorised as low risk ranged from 20% to 71% and the percentage of those categorised as high risk ranged from 29% to 80%. In LN+ patients, the percentage categorised as low risk was 38% to 41% and the percentage categorised as high risk ranged from 59% to 62%. MammaPrint was statistically significantly prognostic for 10-year DRFS in almost all unadjusted analyses of LNO and LN+ patients (as well as in pooled analyses). For LNO patients, 10-year DRFS/DRFI rates for low-risk patients ranged from 80% to 90% (with varying rates of endocrine therapy and chemotherapy use), whereas the reanalysis of a RCT reported 10-year DRFS of 93% with endocrine monotherapy and 83% without endocrine therapy or chemotherapy. Interestingly, although on the whole MammaPrint low-risk 10-year DRFS rates are lower than those for the other in-scope tests, the 93% figure for patients having endocrine monotherapy is more in line with other tests and may better reflect the population used in studies of other tests (ER+, endocrine monotherapy). For LN+ patients, 10-year DRFS rates in low-risk patients ranged from 79% to 91% (with varying rates of endocrine therapy and chemotherapy use). In terms of additional prognostic value, MammaPrint was statistically significantly prognostic for 10-year DRFS/DRFI in multivariable analyses adjusted for clinicopathological risk tools (AOL and NPI) and various combinations of clinicopathological variables in LNO/LN+ and LNO cohorts, whereas adjusted analyses in LN+ cohorts were statistically significant or borderline significant.

### Chemotherapy benefit: MammaPrint

#### Study designs and patients

Two publications have reported the ability of MammaPrint to predict the benefit of chemotherapy. Knauer *et al.*<sup>83</sup> reported a pooled analysis of 541 patients (100% received endocrine therapy, 42% received

chemotherapy) from six consecutive patient series (see *Report Supplementary Material 5, Table 7*). Overall, 90% were ER+ and 89% were HER2-, and half were LN0 and half had one to three positive nodes (LN1–3). In addition, the article by Mook *et al.*<sup>85</sup> reported a pooled analysis of two out of the six patient series from Knauer *et al.*<sup>83</sup> (see *Report Supplementary Material 5, Table 7*), with an extended follow-up (10 years), but restricted to LN1–3 patients (including micrometastases).

### Quality assessment

Both studies were pooled retrospective cohorts in which patients were treated in accordance with usual practice [in addition, one of the six cohorts in Knauer *et al.*<sup>83</sup> was the prospective Microarray-prognostics-in-breast-cancer (RASTER) study,<sup>81</sup> in which patients were treated in accordance with usual practice plus MammaPrint]. For this reason, those who received chemotherapy are likely to be systematically different in terms of known (and potentially unknown) prognostic factors to those who did not, leading to a high risk of confounding. Both studies blinded the test assessors to clinical outcomes, and both used standard outcome definitions. Both studies included a proportion of patients outside the scope (ER- and/or HER2+). See *Report Supplementary Material 5, Table 7*.

### Results

The pooled analysis of six consecutive series by Knauer *et al.*<sup>83</sup> reported that at 5 years, there was a statistically significant effect of chemotherapy in the MammaPrint high-risk group but no statistically significant effect in the low-risk group, although HRs favoured chemotherapy in both groups (*Table 12*). Unadjusted HRs for DRFS (for no chemotherapy vs. chemotherapy) were 0.26 (95% CI 0.03 to 2.02;  $p = 0.20$ ) in the low-risk group and 0.35 (95% CI 0.17 to 0.71;  $p < 0.01$ ) in the high-risk group, whereas unadjusted HRs for BCSS were 0.58 (95% CI 0.07 to 4.98;  $p = 0.62$ ) in the low-risk group and 0.21 (95% CI 0.07 to 0.59;  $p < 0.01$ ) in the high-risk group. Multivariable analyses of the effect of chemotherapy on 5-year BCSS were again statistically significant in the high-risk group (HR 0.21, 95% CI 0.06 to 0.80;  $p = 0.02$ ) but not in the low-risk group (HR not estimable;  $p = 0.98$ ) (see *Table 12*). However, the interaction test for chemotherapy treatment and risk group was not statistically significant ( $p = 0.45$ ; the interaction test appears to relate to 5-year BCSS as opposed to DRFS but this is unclear in the publication<sup>83</sup>). This indicates that the effect of chemotherapy versus no chemotherapy on 5-year BCSS was not statistically significantly different between risk groups. It is unclear whether this interaction test relates to the adjusted or unadjusted analysis.

For the two pooled LNmicro–3 cohorts reported by Mook *et al.*<sup>85</sup> (these were subsets of two of the six cohorts pooled in Knauer *et al.*<sup>83</sup>), the only evidence relating to prediction of chemotherapy benefit was a test of the interaction between chemotherapy treatment and risk group (within a multivariable analysis of 10-year BCSS), which was not statistically significant ( $p = 0.95$ ) (see *Table 12*).

In the analysis of six series,<sup>83</sup> it was unclear whether the interaction test was unadjusted or adjusted, and, if so, for which factors. In the analysis of LN1–3 patients from two series,<sup>85</sup> the interaction test was conducted within a multivariable analysis adjusted for clinicopathological variables.

### Conclusions: MammaPrint chemotherapy benefit

In a pooled analysis of 541 patients (half LN0, half LN1–3) in which patients were treated in accordance with usual practice, the effect of chemotherapy versus no chemotherapy on 5-year DRFS and BCSS was statistically significant in the MammaPrint high-risk group but not in the low-risk group in unadjusted analyses for 5-year DRFS and BCSS and in adjusted analyses for 5-year BCSS. However, the interaction test for chemotherapy treatment and risk group (for 5-year BCSS) was non-significant ( $p = 0.45$ ). A further pooled analysis of two of the above series, restricted to LN1–3 patients, also reported a statistically non-significant interaction between chemotherapy treatment and risk group for 10-year BCSS ( $p = 0.95$ ). The evidence for the ability of MammaPrint to predict chemotherapy benefit is extremely limited; although unadjusted analyses suggest a greater effect of chemotherapy in high-risk groups, adjusted analyses were only reported for one outcome, and the non-significant interaction tests suggest that there was no statistically significant difference in effect of chemotherapy between risk groups.

**TABLE 12** Prediction of chemotherapy responsiveness: MammaPrint

Reference (first author and year)	Cohorts	Population	Percentage of patients in each risk group		Outcome	Low risk			High risk			Adjusted HRs <sup>a</sup>	Interaction tests
			Low	High		No chemotherapy: % risk	Chemotherapy: % risk	HR (95% CI)	No chemotherapy: % risk	Chemotherapy: % risk	HR (95% CI)		
Knauer 2010 <sup>83</sup>	Pooled six series:	<ul style="list-style-type: none"> <li>90% ER+</li> <li>89% HER2–</li> <li>All ET</li> <li>42% chemotherapy</li> </ul>	47	53	DRFS	93	99	0.26 (0.03 to 2.02); $p=0.20$	76	88	0.35 (0.17 to 0.71); $p<0.01$	NR	NR
Pooled cohorts $n=541$	<ul style="list-style-type: none"> <li>NKI, van de Vijver 2002<sup>79</sup></li> <li>Bueno-de-Mesquita 2009<sup>84</sup></li> <li>Mook 2009<sup>85</sup> (LN1–3), NKI plus EIO (Italy)</li> <li>Mook 2010<sup>86</sup> (age 55–71 years)</li> <li>Bueno-de-Mesquita 2007<sup>81</sup> (RASTER)</li> <li>Kok (personal communication within Knauer <i>et al.</i><sup>83</sup> study)</li> </ul>	<ul style="list-style-type: none"> <li>89% HER2–</li> <li>42% chemotherapy</li> <li>LN0, 49%</li> <li>LN1–3, 51%</li> </ul>			5 years	97	99	0.58 (0.07 to 4.98); $p=0.62$	81	94	0.21 (0.07 to 0.59); $p<0.01$	No chemotherapy vs. CT <sup>a</sup> (95% CI): <ul style="list-style-type: none"> <li>Low: CI not estimable, <math>p=0.98</math></li> <li>High: 0.21 (0.06 to 0.80); <math>p=0.02</math></li> </ul>	Interaction <sup>b</sup> (risk group plus chemotherapy): $p=0.45$
Mook 2009 <sup>85</sup> (LNmicro–3)	1. NKI plus EIO (Italy) <sup>85</sup> ( $n=241$ )	<ul style="list-style-type: none"> <li>79/82% ER+</li> <li>84% HER2–</li> </ul>	41	59	10-year BCSS	NR	NR	NR	NR	NR	NR	NR	Interaction (risk group plus chemotherapy, series 1 + 2 pooled, multivariable <sup>a</sup> ): $p=0.95$
Retrospective $n=347$	2. NKI, van de Vijver 2002 <sup>79</sup> ( $n=106$ )	<ul style="list-style-type: none"> <li>73/23% ET</li> <li>56/70% chemotherapy</li> <li>LNmicro–3</li> </ul>											

ET, endocrine therapy; NKI, Netherlands Cancer Institute; NR, not reported.

a Adjusted for:

- Knauer 2010 – age, tumour size, nodal status, grade, ER, PR, endocrine therapy, chemotherapy.
- Mook 2010 – age, tumour size, nodal status, grade, ER, HER2, surgery, endocrine therapy, chemotherapy.

b Unclear whether interaction test in Knauer 2010 relates to adjusted or unadjusted analysis.

## Clinical utility: MammaPrint

### Overview

Two studies reported evidence relating to clinical utility of MammaPrint (the impact of prospective use of the test on clinical outcomes). Microarray In Node-negative Disease may Avoid ChemoTherapy (MINDACT) is a RCT of MammaPrint versus clinical practice.<sup>98</sup> RASTER<sup>81,99,100</sup> is a prospective observational study in which patients were treated in accordance with usual practice plus MammaPrint. As these two studies are very different in design, they are reported separately in the following sections.

This section of the report summarises the main points; a full description can be found in *Report Supplementary Material 5*.

### Clinical utility randomised controlled trial: MINDACT

#### Study design

MINDACT (Cardoso *et al.*<sup>98</sup>) is a partially randomised prospective study of MammaPrint versus clinical practice. Patients with discordant risk scores (high risk/low risk or low risk/high risk) as assessed by MammaPrint and mAOL (mAOL was calculated *HER2* status as well as the usual grade, nodal status and tumour size, and is not a tool used in clinical practice in the UK, which limits the generalisability of findings of this trial) were randomised to chemotherapy or no chemotherapy; this also means that discordant-risk patients were randomised to treatment determined by MammaPrint or treatment determined by mAOL.

Patients with concordant risk were not randomised, but were followed as prospective cohorts. High/high-risk patients (via both MammaPrint and mAOL) were recommended to receive chemotherapy, whereas no chemotherapy was recommended for low/low-risk patients.

The primary aim was to determine whether or not patients who were at high-clinical and low-MammaPrint risk could avoid chemotherapy by comparing outcomes for patients randomised to chemotherapy or no chemotherapy. The results were also presented for low-clinical-risk, high-MammaPrint-risk patients. Secondary analyses included an analysis of discordant patients in accordance with treatment group (chemotherapy vs. no chemotherapy) and for all patients when chemotherapy was recommended in accordance with clinical risk or with MammaPrint risk. The percentage of patients assigned to chemotherapy with each strategy was also reported.

#### Patients and tests

MINDACT enrolled 6693 patients from nine European countries (see *Report Supplementary Material 5, Table 9*, for details of group assignments). Of these patients, 88% were hormone-receptor-positive and 90% were *HER2*-; 79% were LN0 and 21% were LN1–3. However, this varied by group (see *Report Supplementary Material 5, Table 9*).

#### Quality assessment

Randomisation sequence and allocation concealment were judged as having a low risk of bias. No details of blinding were reported (see *Report Supplementary Material 5, Table 10*). Intention-to-treat (ITT) and per-protocol analyses were reported. Some patients did not adhere to their recommended chemotherapy or no chemotherapy allocation. Other patients had a change in clinical risk group owing to initial incorrect reporting of clinical characteristics, or a change in MammaPrint risk group owing to a change in the RNA extraction solution that affected the calculation of risk group. For the ITT analysis, patients were analysed in their originally allocated clinical/MammaPrint risk groups and in their randomised treatment groups. Per-protocol analysis excluded patients who were ineligible, were non-adherent to chemotherapy recommendations or who had a change in their clinical or MammaPrint risk group. This report uses ITT results (when available).

## Results

### ***High-clinical-risk, low-MammaPrint-risk group***

In this group ( $n = 1497$ ; 52% LN0), 5-year DMFS was 95.9% (95% CI 94.0% to 97.2%) with chemotherapy and 94.4% (95% CI 92.3% to 95.9%) without chemotherapy; this was an absolute difference of 1.5% favouring chemotherapy, although the HR was not statistically significant (adjusted HR 0.78, 95% CI 0.50 to 1.21;  $p = 0.267$ ). Similar differences between chemotherapy and no chemotherapy were reported for 5-year DMFI, DFS and OS, as well as among both LN0 and LN1–3 patients and a LN0, HR+, HER2– subgroup (Table 13). Statistically, this met the primary objective in that the lower bound of the 95% CI for 5-year DMFS in the no-chemotherapy group was  $\geq 92\%$ . This finding was interpreted by the authors as showing little difference in outcomes for chemotherapy versus no chemotherapy, implying that patients who were at high-clinical but low-MammaPrint risk could potentially avoid chemotherapy. Clinical advice to the EAG suggests that chemotherapy would usually only be indicated when it is likely to provide an absolute improvement in 5-year DRFS of 2–3%, which suggests that it may be reasonable to withhold chemotherapy in patients with high-clinical, low-MammaPrint risk given the above absolute difference in 5-year DRFS of 1.5% for chemotherapy versus no chemotherapy.

### ***Low-clinical-risk, high-MammaPrint-risk group***

Among these patients ( $n = 690$ ; 98% LN0) (see Table 13), 5-year DMFS was 95.8% (95% CI 92.9% to 97.6%) with chemotherapy and 95.0% (95% CI 91.8% to 97.0%) without chemotherapy, an absolute difference of 0.8% (adjusted HR 1.17, 95% CI 0.59 to 2.28;  $p = 0.657$ ). These findings could be interpreted as showing that use of MammaPrint in low-clinical-risk patients could lead to more patients being prescribed chemotherapy but not receiving a survival benefit from treatment.

### ***Non-randomised concordant-risk groups***

Patients with low/low-risk (recommended no chemotherapy) had a 5-year DMFS of 97.6% (95% CI 96.9% to 98.1%). Conversely, patients with high/high-risk (recommended chemotherapy) had a 5-year DMFS of 90.6% (95% CI 89.0% to 92.0%). The results for DFS and OS followed a similar pattern (see Table 13).

### ***Estimated outcomes in accordance with clinical and MammaPrint treatment strategies***

Additional analyses assessed strategies in which chemotherapy recommendations for all patients were determined by either clinical risk or MammaPrint risk. These included concordant (non-randomised) and discordant (randomised) patients who had treatment that matched either their clinical risk (treatment determined by clinical risk group) or MammaPrint risk (treatment determined by MammaPrint risk group). Of all 6693 patients, 3356 (50%) were at high clinical risk using mAOL and 2398 (36%) were at high MammaPrint risk (data not tabulated). Therefore 14% fewer (958/6693) patients were categorised as being at high risk using MammaPrint than using mAOL, and of those at high clinical risk, 46% (1550/3356) could be reclassified to low risk by MammaPrint. The 5-year DMFS rate was very similar between the clinical strategy (5-year DMFS rate 95.0%) and the MammaPrint strategy (5-year DMFS rate 94.7%). This was interpreted as the MammaPrint strategy leading to little difference in outcomes while sparing many patients from chemotherapy. Given the results in the low-clinical-risk group (in which treatment in accordance with MammaPrint risk groups would result in more patients receiving chemotherapy but with no DMFS advantage), the most advantageous strategy may be to only test clinical high-risk patients with MammaPrint. However, the comparator in this study was mAOL, and it is unclear whether or not the same would be true for other clinical risk scores.

### ***Multivariable analysis***

In a multivariable analysis adjusted for chemotherapy use, clinical risk and patient and tumour characteristics, MammaPrint low/high-risk grouping was statistically significantly associated with 5-year DMFS (HR for high vs. low-risk 2.41, 95% CI 1.79 to 3.26;  $p < 0.001$ ).

TABLE 13 Clinical utility of MammaPrint (MINDACT)

Study (first author and year)	Subgroup	n	Population	Nodal status	Outcome	Percentage risk of outcome (95% CI)		HR adjusted <sup>a</sup> (95% CI)	Absolute difference (95% CI)
						No chemotherapy	Chemotherapy		
<b>High clinical, low MammaPrint group (randomised to chemotherapy or no chemotherapy; ITT<sup>b</sup>)</b>									
<i>Node negative and node positive</i>									
Cardoso 2016 <sup>38</sup>	High mAOL, low MammaPrint	1497	98% HR+, 92% HER2-	LN0, 52%; LN1-3, 48%	5-year DMFS	94.4 (92.3 to 95.9)	95.9 (94.0 to 97.2)	0.78 (0.50 to 1.21); <i>p</i> = 0.267	1.5%
					5-year DRFI	95.3 (93.4 to 96.6)	96.6 (94.8 to 97.8)	0.76 (0.47 to 1.22); <i>p</i> = 0.253	1.3%
					5-year DFS	90.1 (87.5 to 92.1)	92.9 (90.5 to 94.7)	0.71 (0.50 to 1.01); <i>p</i> = 0.055	2.8%
					5-year OS	97.0 (95.4 to 98.1)	98.4 (97.0 to 99.1)	0.69 (0.35 to 1.35); <i>p</i> = 0.278	1.4%
<i>Node negative</i>									
Cardoso 2016 <sup>38</sup>	High mAOL, low MammaPrint	787	NR	LN0	5-year DMFS	93.2 (90.1 to 95.4)	95.7 (93.0 to 97.4)	0.69 (0.39 to 1.21); <i>p</i> = 0.193	2.5%
		699	All HR+, all HER2-	LN0	5-year DMFS	93.9 (90.6 to 96.1)	95.5 (92.5 to 97.3)	0.80 (0.44 to 1.45); <i>p</i> = 0.456	1.6%
<i>Node positive</i>									
Cardoso 2016 <sup>38</sup>	High mAOL, low MammaPrint	709	NR	LN1-3	5-year DMFS	95.6 (92.7 to 97.4)	96.3 (93.1 to 98.1)	0.88 (0.42 to 1.82); <i>p</i> = 0.724	0.7%
<b>Low clinical, high MammaPrint group (randomised to chemotherapy or no chemotherapy; ITT<sup>b</sup>)</b>									
<i>Node negative and node positive</i>									
Cardoso 2016 <sup>38</sup>	Low mAOL, high MammaPrint	690	90% HR+, 88% HER2-	LN0, 98%; LN1-3, 2%	5-year DMFS	95.0 (91.8 to 97.0)	95.8 (92.9 to 97.6)	1.17 (0.59 to 2.28); <i>p</i> = 0.657	0.8%
					5-year DRFI	95.6 (92.5 to 97.5)	98.1 (95.7 to 99.1)	0.63 (0.27 to 1.47); <i>p</i> = 0.282	2.5%
					5-year DFS	90.1 (86.1 to 93.0)	92.1 (88.3 to 94.6)	0.87 (0.53 to 1.45); <i>p</i> = 0.603	2.0%
					5-year OS	97.8 (95.5 to 99.0)	97.1 (94.5 to 98.5)	1.28 (0.54 to 3.02); <i>p</i> = 0.578	-0.7%

continued

**TABLE 13** Clinical utility of MammaPrint (MINDACT) (*continued*)

Study (first author and year)	Subgroup	n	Population	Nodal status	Outcome	Percentage risk of outcome (95% CI)		HR adjusted <sup>a</sup> (95% CI)	Absolute difference (95% CI)
						No chemotherapy	Chemotherapy		
<i>Node negative</i>									
Cardoso 2016 <sup>98</sup>	Low mAOL, high MammaPrint	635	NR	LN0	5-year DMFS	95.1 (91.9 to 97.1)	96.0 (93.1 to 97.7)	1.09 (0.54 to 2.19); p=0.815	0.9%
		534	All HR+, all HER2-	LN0	5-year DMFS	95.5 (91.6 to 97.6)	95.1 (91.5 to 97.2)		
<i>Node positive</i>									
Cardoso 2016 <sup>98</sup>	Low mAOL, high MammaPrint	NR (number too small)	NR	LN1-3	5-year DMFS	NR	NR	NR	NR
<b>Outcomes for non-randomised groups<sup>b</sup></b>									
<i>Low clinical, low MammaPrint (node negative and node positive)</i>									
Cardoso 2016 <sup>98</sup>	Low mAOL, low MammaPrint	2745	100% HR+, 96% HER2-	LN0, 94%; LN1-3, 6%	5-year DMFS	97.6 (96.9 to 98.1)	N/A		
					5-year DFS	92.8 (91.7 to 93.7)	N/A		
					5-year OS	98.4 (97.8 to 98.9)	N/A		
<i>High clinical, high MammaPrint (node negative and node positive)</i>									
Cardoso 2016 <sup>98</sup>	High mAOL, high MammaPrint	1806	62% HR+, 81% HER2-	LN0, 74%; LN1-3, 26%	5-year DMFS	N/A	90.6 (89.0 to 92.0)		
					5-year DFS	N/A	85.3 (83.4 to 87.0)		
					5-year OS	N/A	94.7 (93.4 to 95.7)		

N/A, not applicable; NR, not reported.

a HRs adjusted for institution, risk group, ER, PR, nodal status, age, HER2, axillary treatment, surgery; HR below 0 favours chemotherapy.

b ITT analysis includes initially allocated risk groups and treatment assignment, irrespective of adherence to treatment.

### Conclusions: randomised controlled trial of clinical utility for MammaPrint (MINDACT)

MINDACT randomised patients with discordant MammaPrint and mAOL risks to chemotherapy or no chemotherapy. For patients who were high-clinical, low-MammaPrint risk, 5-year DMFS was 95.9% with chemotherapy and 94.4% without chemotherapy, an absolute difference of 1.5%. This raises the possibility of avoiding chemotherapy in these patients. In patients who were low-clinical, high-MammaPrint risk, 5-year DMFS was 95.8% with chemotherapy and 95.0% without chemotherapy, an absolute difference of 0.8%. This could be interpreted as showing that MammaPrint may not be useful in this group as it would increase chemotherapy rates without improving outcomes. However, the comparator was mAOL, and it is unclear whether or not the same would be true for other clinical risk measures.

### Clinical utility observational study: RASTER

#### *Study design, patients and tests*

RASTER (Drukker *et al.*,<sup>99</sup> Drukker *et al.*,<sup>100</sup> Bueno-de-Mesquita *et al.*<sup>81</sup> and Vliek *et al.*<sup>101</sup>) is a prospective observational study in which LN0 ( $n = 427$ , 80% ER+, 84% HER2–) patients in the Netherlands were treated in accordance with MammaPrint plus usual clinical practice [2004 Dutch Institute of Healthcare Improvement (Central Accompaniment Organization) guidelines<sup>102</sup> and clinician and patient preference]. The aims were to assess the impact of MammaPrint on treatment decisions and to prospectively record outcomes for patients categorised as being at high or low risk via MammaPrint, via clinical risk tools and for various combinations of MammaPrint risk and clinical risk. An additional analysis conducted retrospectively in LN+ patients ( $n = 164$ ) was reported separately (Vliek *et al.*<sup>103</sup>). Frozen tumour samples were used<sup>99</sup> in the LN0 study and FFPE samples were used in the retrospective analysis of LN+ patients.<sup>103</sup> MammaPrint 70-gene microarray was used, stating that cut-off points were the same as in previous studies<sup>99</sup> (see *Report Supplementary Material 5, Table 13*).

#### *Quality assessment*

Because RASTER was not a RCT, it was judged to be at a high risk of bias using standard RCT criteria (see *Report Supplementary Material 5, Table 14*). Prognostic results from this study are confounded by the differing rates of chemotherapy in different risk groups (usually more chemotherapy in the high-risk group than in the low-risk group).

### Results for lymph node-negative patients

#### *Results for MammaPrint (in conjunction with Central Accompaniment Organization guidelines and patient/clinician preference)*

In LN0 patients ( $n = 427$ ), 51% were at low risk (of whom 15% received chemotherapy) and 49% were at high risk (of whom 81% received chemotherapy). At 5 years, DRFI was 97.0% for low-risk patients and 91.7% for high-risk patients ( $p = 0.03$  between groups, HR not reported) (*Table 14*).<sup>99,100</sup> The 10-year DRFI was 93.7% for low-risk and 86.8% for high-risk patients (HR 1.4, 95% CI 1.0 to 1.9). Results at 10 years were similar for the 342 ER+ patients, although not statistically significant (Vliek *et al.*<sup>101</sup>) (see *Table 14*). The 5-year OS was not statistically significantly different between MammaPrint groups ( $p = 0.35$ , HR not reported) (see *Report Supplementary Material 5, Table 15*).<sup>99,100</sup>

#### *Results for clinical risk tools*

MammaPrint results were compared with the results of the NPI and Predict Plus clinical risk tools applied retrospectively to the data (see *Tables 14 and 15*). Results were similar to MammaPrint for proportions in low- and high-risk categories and for 5-year DRFI rates. Both NPI and Predict Plus showed a significant difference between groups ( $p = 0.03$  and  $p = 0.004$ , respectively).<sup>99,100</sup>

**TABLE 14** Clinical utility of MammaPrint (RASTER study): DRFI<sup>a</sup> in node-negative patients

Study	Subgroup	Population: ET/chemotherapy	Nodal status	Outcome	Test or comparator	Percentage of patients per group		Percentage chemotherapy per group		Percentage DRFI risk: 0–5 years		Percentage DRFI risk: 0–10 years		HR (95% CI); <i>p</i> -value	
						Low	High	Low	High	Low	High	Low	High	0–5 years	0–10 years
<b>Node negative</b>															
RASTER <sup>99–101</sup>	All patients, <i>n</i> = 427	<ul style="list-style-type: none"> <li>80% ER+</li> <li>84% HER2–</li> <li>43% ET</li> <li>47% chemotherapy</li> </ul>	LN0	DRFI	MammaPrint	51	49	15	81	97.0	91.7	93.7	86.8	<i>p</i> = 0.03	1.4 (1.0 to 1.9)
LN0					AOL	31	69	18	60	96.7	93.4	NR	NR	<i>p</i> = 0.24	NR
					NPI	58	42	21	84	96.7	91.3	NR	NR	<i>p</i> = 0.03	NR
					Predict Plus (University of Cambridge, Cambridge, UK)	53	47	20	78	96.8	91.7	NR	NR	<i>p</i> = 0.004	NR
					mAOL	57	43	NR	NR	NR	NR	91.7	88.2	NR	1.4 (0.8 to 2.6)
<b>ER+ patients</b>															
RASTER <sup>94,101</sup>	ER+ patients, <i>n</i> = 342	<ul style="list-style-type: none"> <li>All ER+</li> <li>HER2 NR</li> </ul>	LN0	DRFI	MammaPrint	63	37	NR	NR	NR	NR	93.6	88.8	NR	1.6 (0.8 to 3.3)
LN0					mAOL	NR	NR	NR	NR	NR	NR	91.6	91.9	NR	NR
<b>High clinical risk</b>															
RASTER <sup>99–101</sup>	AOL high, <i>n</i> = 295	<ul style="list-style-type: none"> <li>ER+/ER–</li> <li>HER2+/HER2–</li> </ul>	LN0	DRFI	MammaPrint	42	58	24	87	98.4	89.8	NR	NR	NR	NR
LN0	NPI high, <i>n</i> = 179					25	75	57	93	95.5	89.9	NR	NR	NR	NR
	Predict Plus high, <i>n</i> = 199					25	75	41	91	93.9	91.0	NR	NR	NR	NR
	mAOL high, <i>n</i> = 183					25	75	NR	NR	NR	NR	90.9	87.3	NR	NR
<b>High clinical risk, untreated</b>															
RASTER <sup>99,100</sup>	AOL high; no chemotherapy ( <i>n</i> = 117)	<ul style="list-style-type: none"> <li>ER+/ER–</li> <li>HER2+/HER2–</li> </ul>	LN0	DRFI	MammaPrint	80	20	0	0	98.9	NR	NR	NR	NR	NR
LN0	AOL high; no ET/chemotherapy ( <i>n</i> = 75)					93	7	0	0	100.0	NR	NR	NR	NR	NR

Study	Subgroup	Population: ET/chemotherapy	Nodal status	Outcome	Test or comparator	Percentage of patients per group		Percentage chemotherapy per group		Percentage DRFI risk: 0–5 years		Percentage DRFI risk: 0–10 years		HR (95% CI); <i>p</i> -value	
						Low	High	Low	High	Low	High	Low	High	0–5 years	0–10 years
<b>Low clinical risk</b>															
RASTER <sup>99–101</sup>	AOL low, <i>n</i> = 132	<ul style="list-style-type: none"> <li>● ER+/ER–</li> <li>● HER2+/HER2–</li> </ul>	LN0	DRFI	MammaPrint	72	28	3	57	95.3	100.0	NR	NR	NR	NR
LNO	NPI low, <i>n</i> = 248					71	29	5	59	97.4	95.3	NR	NR	NR	NR
	Predict Plus low, <i>n</i> = 228					75	25	8	57	98.0	93.9	NR	NR	NR	NR
	mAOL low, <i>n</i> = NR					NR	NR	NR	NR	NR	NR	94.4	88.5	NR	NR
<b>Low clinical risk, untreated</b>															
RASTER <sup>99–100</sup>	AOL low; no chemotherapy ( <i>n</i> = 108)	<ul style="list-style-type: none"> <li>● ER+/ER–</li> <li>● HER2+/HER2–</li> </ul>	LN0	DRFI	MammaPrint	85	15	0	0	95.1	NR	NR	NR	NR	NR
LNO	AOL low; no ET/chemotherapy ( <i>n</i> = 93)					95	5	0	0	95.0	NR	NR	NR	NR	NR

ET, endocrine therapy; NR, not reported; RASTER, MicroarRay PrognoStics in Breast CancER study.

a In RASTER, definition of DRFI includes DR and BC death as events, which is more similar to definitions of DRFS/DMFS in most studies in this review.

**TABLE 15** Clinical utility of MammaPrint (RASTER study): additional prognostic value in node-negative patients

Study	Subgroup	Population	Nodal status	ET/chemotherapy	Outcome	Test or comparator	Percentage of patients per group		Percentage chemotherapy per group		C-index (AUC)	Increase in C-index (AUC) over clinicopathological factors
							Low	High	Low	High		
<b>Node negative</b>												
RASTER <sup>99-101</sup>	All patients, n = 427	<ul style="list-style-type: none"> <li>80% ER+</li> <li>84% HER2-</li> </ul>	LNO	<ul style="list-style-type: none"> <li>43% ET</li> <li>47% chemotherapy</li> </ul>	5-year DRFI	MammaPrint	51	49	15	81	NR	
						AOL	31	69	18	60	0.532	
						AOL plus MammaPrint	NR	NR	NR	NR	0.619	p = 0.03
						NPI	58	42	21	84	0.591	
						NPI plus MammaPrint	NR	NR	NR	NR	0.638	p = 0.05
						Predict Plus	53	47	20	78	0.627	
Predict Plus plus MammaPrint	NR	NR	NR	NR	0.662	p = 0.27						

ET, endocrine therapy; NR, not reported; RASTER, MicroarRAY PrognoSics in Breast CancER study.

Conversely, AOL categorised more patients as high risk compared with MammaPrint, NPI or Predict Plus, (69% compared with 49%, 42% and 47%, respectively). High-risk AOL patients had a lower chemotherapy rate (60% compared with 81%, 84% and 78%, respectively), and 5-year DRFI was similar for the low-risk group (96.7% compared with 97.0%, 96.7 and 96.8%, respectively) but was higher in the high-risk group (93.4%, compared with 91.7%, 91.3% and 91.7%, respectively). The difference between AOL low- and high-risk groups was  $p = 0.24$  (see *Table 14*).<sup>99,100</sup> mAOL categorised similar numbers of patients as being at high risk and low risk as MammaPrint, NPI and Predict Plus. The 10-year DRFI for mAOL was more favourable for the low-risk group than the high-risk group, but this was not statistically significant (HR 1.4, 95% CI 0.8 to 2.6) and any difference was lost when restricting to ER+ patients (see *Table 14* and Vliek *et al.*<sup>101</sup>).

### ***MammaPrint results for patients at high/low clinical risk***

Results by MammaPrint risk group for patients at a high or low clinical risk in accordance with NPI, Predict Plus and AOL are also presented. The results are presented in detail in *Report Supplementary Material 5*. In summary, observed 5-year DRFI rates were lower in patients with high NPI risk/low MammaPrint risk and in patients with high Predict Plus risk/low MammaPrint risk (5-year DRFI rates 95.5% and 93.9%, respectively) than in the whole MammaPrint low-risk group (5-year DRFI rate 97.0%), and were similar in the high-clinical-risk/high-MammaPrint-risk groups (5-year DRFI rates 89.9% and 91.0%, respectively) compared with a 5-year DRFI rate of 91.7% in the MammaPrint high-risk group. AOL classified more patients as being at high risk than NPI and Predict Plus and had a 5-year DRFI of 90.6%; a higher proportion of these patients were reclassified by MammaPrint as being at low risk.

### ***Additional prognostic value of MammaPrint***

*Table 15* shows C-indices (AUC) for clinical risk tools only and in addition to MammaPrint. The addition of MammaPrint to AOL or NPI statistically significantly increased the C-index (AUC) ( $p = 0.03$  and  $p = 0.05$ , respectively), whereas the addition of MammaPrint to Predict Plus did not statistically significantly increase the C-index (AUC) ( $p = 0.27$ ) (see *Table 15*).<sup>100</sup>

### **Results for lymph node-positive patients**

MammaPrint was retrospectively conducted in 164 LN+ patients (*Table 16*). Over 95% of patients received chemotherapy. MammaPrint categorised 48% of LN1–3 patients as low risk. The 5-year DRFI was 98.4% for low-risk and 86.9% for high-risk patients, whereas 10-year DRFI was 94.9% for low-risk and 80.7% for high-risk patients, showing a statistically significant difference between groups (HR 4.7, 95% CI 1.3 to 16.2). A comparison was made with the mAOL, although this analysis included 30 additional patients with LN > 3 who were automatically classed as high risk. The mAOL categorised only 14% of patients as being at low risk; 10-year DRFI was 94.4% for low-risk and 85.8% for high-risk patients, which was not statistically significantly different (HR 3.7, 95% CI 0.5 to 28.5). Within the mAOL high-risk group, 10-year DRFI was statistically significantly better in MammaPrint low-risk (95.2%) than high-risk (79.6%) patients (HR 4.8, 95% CI 1.1 to 21.4).<sup>101</sup>

### **Conclusions: observational study of clinical utility for MammaPrint (RASTER)**

RASTER is a prospective observational study in which patients were treated in accordance with MammaPrint plus usual clinical practice (LN0) or in accordance with usual clinical practice (LN+). The 5-year DRFI for LN0 patients was 97.0% for low-risk patients (15% had chemotherapy) and 91.7% for high-risk patients (81% received chemotherapy). The 10-year DRFI for LN0 patients was 93.7% for low-risk and 86.8% for high-risk patients. The DRFI rates in the MammaPrint low-risk group may be considered sufficiently low for these patients to avoid chemotherapy. MammaPrint provided additional prognostic information over AOL and NPI, but not over Predict Plus when considering C-indices. Estimates of prognostic performance between risk groups are likely to be affected by the differing rates of chemotherapy in each group and the fact that chemotherapy use was influenced by MammaPrint.

**TABLE 16** Clinical utility of MammaPrint (RASTER study): DRFI<sup>a</sup> in node-positive patients

Study (first author and year)	Subgroup	Population: ET/chemotherapy	Nodal status	Outcome	Test or comparator	Percentage of patients per group		Percentage chemotherapy per group		Percentage DRFI risk				HR (95% CI), <i>p</i> -value	
						Low	High	Low	High	0–5 years		0–10 years		30–5 years	0–10 years
<b>Node positive</b>															
RASTER LN+, Vliek 2017 <sup>101</sup>	LN1–3, <i>n</i> = 134	<ul style="list-style-type: none"> <li>ER+/ER–</li> <li>HER2NR</li> <li>95% chemotherapy</li> </ul>	LN1–3	DRFI	MammaPrint	48	52	NR	NR	98.4	86.9	94.9	80.7	NR	4.7 (1.3 to 16.2); <i>p</i> = 0.008
	All (three were missing data), <i>n</i> = 161	<ul style="list-style-type: none"> <li>83% ER+</li> <li>HER2 NR</li> <li>&gt;95% chemotherapy</li> </ul>	<ul style="list-style-type: none"> <li>LN1–3, 82%</li> <li>LN &gt; 3, 18%</li> </ul>		mAOL	14	86	NR	NR	100	90.8	94.4	85.8	NR	3.7 (0.5 to 28.5); <i>p</i> = 0.173
<b>High clinical risk</b>															
RASTER LN+, Vliek 2017 <sup>101</sup>	mAOL high risk, <i>n</i> = 109	<ul style="list-style-type: none"> <li>ET NR</li> <li>&gt;95% chemotherapy</li> </ul>	LN+	DRFI	MammaPrint	40	60	NR	NR	97.7	86.1	95.2	79.6	NR	4.8 (1.1 to 21.4)
ET, endocrine therapy; NR, not reported; RASTER, MicroarRay PrognoS <sup>T</sup> ics in Breast CancER study.															
a In RASTER, definition of DRFI includes DR and BC death as events, which is more similar to definitions of DRFS/DMFS in most studies in this review.															
<b>Note</b>															
mAOL includes <i>HER2</i> .															

## Results: Prosigna

A description of Prosigna and its development is given in *Report Supplementary Material 6*. A summary of the key results from the review is provided in this section. A detailed narrative synthesis of all study results is also provided in *Report Supplementary Material 6*.

Prosigna is based on a ROR score called ROR-PT, which incorporates the PAM50 gene signature, a weighting for a proliferation score (P, a subset of the 50 genes) and information on tumour size (T). Nodal status is then used when converting the score into a risk category. The results for the commercial test using nCounter and for research-based versions using other methods (e.g. RT-qPCR) are reported here. Studies assessing ROR-PT via whole-transcriptome microarray are summarised in *Report Supplementary Material 10*. ROR-S (subtype), ROR-T/ROR-C (subtype and tumour size) and ROR-P (subtype and proliferation score) were outside the scope of this review. Within this section, the test is referred to as ROR-PT.

### Prognostic performance: Prosigna

#### Study designs: Prosigna prognostic performance

Eight data sets were used to assess the prognostic performance of ROR-PT (see *Report Supplementary Material 6, Table 1*). These included six reanalyses of RCTs [TransATAC,<sup>38,46</sup> Austrian Breast and Colorectal Cancer Study Group (ABCSG) 8,<sup>104,105</sup> Cancer and Leukemia Group B (CALGB 9741),<sup>106</sup> National Cancer Institute of Canada (NCIC) MA.21,<sup>107</sup> Grupo Español de Investigación en Cáncer de Mama (GEICAM) 9906<sup>108,109</sup> and NCIC MA.12<sup>110</sup>] and two retrospective analyses of prospective cohorts [the Danish Breast Cancer Cooperative Group (DBCG) cohort<sup>111–114</sup> and two analyses of the British Columbia cohort<sup>115,116</sup>].

#### Patients: Prosigna prognostic performance

Two of the RCTs (TransATAC<sup>38,46</sup> and ABCSG 8,<sup>104,105</sup> total  $n = 2252$ ) and the two retrospective analyses (total  $n = 3508$ ) included patients who were all/mostly ER+ and HER2– and received endocrine monotherapy. The other four RCTs<sup>106–110</sup> (total  $n = 3358$ ) included higher-risk patients (not restricted to ER+ and HER2–, higher proportion LN+) and all received chemotherapy (see *Report Supplementary Material 6, Table 1*). Two studies recruited only LN+ patients (CALGB 9741<sup>106</sup> and GEICAM 9906<sup>108,109</sup>), one recruited LN0 patients (DBCG<sup>111–114</sup>) and the remainder recruited both LN0 and LN+ patients.

#### Tests and comparators: Prosigna prognostic performance

Four analyses of RCTs<sup>38,46,104–107</sup> and two analyses of prospective cohorts<sup>111–115</sup> measured ROR-PT using the nCounter device, and two analyses of RCTs<sup>108–110</sup> and one of a prospective cohort<sup>116</sup> used RT-qPCR (see *Report Supplementary Material 6, Table 1*). The cut-off points used to define risk groups varied across studies, and some analyses assessed ROR-PT as a continuous score (see *Report Supplementary Material 6, Table 1*).

#### Quality assessment: Prosigna prognostic performance

See *Report Supplementary Material 6, Table 1*. All analyses excluded some patients recruited to the original trial or cohort. Blinding of test assessors to outcomes was reported in five analyses. All used standardised outcomes.

### Results: Prosigna prognostic performance

#### Distribution of patients by risk group

For LN0 patients, the percentages categorised as low risk were reported in two analyses: 55% in TransATAC<sup>46</sup> and 48% in ABCSG 8.<sup>104,105</sup> Among LN+ patients, far fewer patients were categorised as low risk: 8% in TransATAC,<sup>46</sup> 4% in ABCSG 8,<sup>104,105</sup> 19% in GEICAM 9906<sup>108,109</sup> and 25% in DBCG.<sup>112</sup> The percentages of patients categorised as intermediate risk were 30%<sup>46</sup> and 32%<sup>104,105</sup> in LN0 patients and ranged from 27% to 56% in LN+ patients.<sup>46,104,105,108,109,112</sup> The number of patients who are likely to be prescribed chemotherapy on the basis of their test result will depend on how intermediate-risk patients are handled and whether or not they would be handled in the same way in LN0 and LN+ groups.

**Prognostic performance: unadjusted analyses**

For LN0 patients, ROR-PT was statistically significantly prognostic for DRFS/DFMS/DRFI in all three data sets (TransATAC,<sup>46</sup> ABCSG 8<sup>104,105</sup> and DBCG<sup>112</sup>). HRs and *p*-values between groups are reported in many differing formats and time points so are summarised in *Table 17* rather than in the text. ROR-PT was also statistically significantly prognostic for late (5- to 15-year) recurrence in the one study reporting this.<sup>104,105</sup>

For LN+ patients, ROR-PT was statistically significantly prognostic for 10-year DRFS/DFMS/DRFI in all four data sets (TransATAC,<sup>46</sup> ABCSG 8,<sup>104,105</sup> DBCG<sup>112</sup> and GEICAM 9906<sup>108,109</sup>). ROR-PT was also statistically significantly prognostic for late (5- to 10-year) recurrence in the two studies reporting this.<sup>104,105,112,113</sup>

Other outcomes and subgroups (pre/post menopausal, ductal/lobular cancer) are reported in *Report Supplementary Material 6*.

**Additional prognostic value**

In terms of additional prognostic value (*Table 18*), multivariable analyses of two data sets (ABCSG 8 and DBCG)<sup>104,111,112</sup> showed that ROR-PT was an independent prognostic parameter for 10-year DMFS/DRFS after adjustment for clinicopathological variables across LN0/LN+ and LN+ patients. Two data sets (TransATAC<sup>46</sup> and ABCSG 8<sup>104</sup>) reported an increase in likelihood ratio  $\chi^2$  for ROR-PT plus CTS/clinical linear predictor (CLP)/NPI over CTS/CLP/NPI only; this increase was statistically significant in LN0 and LN+ patients in ABCSG 8,<sup>104</sup> and in TransATAC the increase was statistically significant in LN0 patients and borderline significant in LN+ patients.<sup>46</sup> One study reported an increase in likelihood ratio  $\chi^2$  (*p* < 0.0001) for ROR-PT over clinicopathological variables in DBCG, a mixed cohort of LN+/LN0 patients.<sup>112</sup>

**Conclusions: Prosigna prognostic performance**

Based on six reanalyses of RCTs and two retrospective analyses of prospective cohorts, Prosigna/ROR-PT was statistically significantly prognostic for unadjusted analyses of 10-year DRFS/DRFI in LN0 and LN+ patients. Among LN0 patients, approximately 50% were categorised as low risk, 30% as intermediate risk and 15% to 20% as high risk. Among LN+ patients, 4% to 25% were at low risk, 27% to 56% were at intermediate risk and 26% to 62% were at high risk. The 10-year DRFS/DRFI rates for low-risk patients were 95% to 97% in three studies of LN0 patients (all endocrine therapy only), and in LN+ patients these were 100% in two studies (endocrine therapy only) and 92% in one study (all endocrine therapy and chemotherapy). ROR-PT added prognostic information over clinicopathological variables or CTS/CLP/NPI in three studies; this was statistically significant in LN0 patients and either significant or borderline significant in LN+ patients.

**Results: EndoPredict and EndoPredict Clinical****Development: EndoPredict and EndoPredict Clinical**

EndoPredict and EPclin risk scores were trained on 964 ER+, HER2- endocrine-treated samples (65% node negative) from a range of sources (Filipits *et al.*<sup>117</sup>). EndoPredict generates an EndoPredict score based on the gene signature alone. The EPclin score is calculated from the EndoPredict score plus information on tumour size and nodal status.

**Prognostic performance: EndoPredict and EndoPredict Clinical****Study characteristics**

The prognostic value of EPclin was assessed in three reanalyses of RCTs,<sup>36,46,108,109,118-120</sup> which included four RCTs (total *n* = 3135): UK patients from TransATAC (*n* = 878), the ABCSG 6 and ABCSG 8 (total *n* = 1702) and the Spanish GEICAM 9906 trial (*n* = 555). All recruited only, or reported a subgroup of, patients who were ER+ and HER2-. One reported on LN0 patients (total *n* = 680)<sup>36,39,46</sup> and two<sup>36,46,108,109</sup> on LN+ patients (total *n* = 753; one<sup>108,109</sup> included 36% patients with at least three positive nodes). One reported on patients unselected by lymph node status,<sup>120</sup> and one on both LN0 and LN1-3 together;<sup>46</sup> additional analyses<sup>118</sup> were provided to the EAG as commercial-in-confidence data and cannot be reported

TABLE 17 Prognostic performance of Prosigna: DRFS/DRFI<sup>a</sup>

Reference (first author and year)	Cohort, design, country	Population	Nodal status	ET/chemotherapy	Test	Percentage of patients per group			Percentage DRFS/DRFI risk						DMFS/DRFS: <sup>a</sup> HR (95% CI)	
						Low	Intermediate	High	0–5 years			0–10 years				
<b>LN status mixed</b>																
<i>100% ET monotherapy</i>																
Sestak 2017 (data request) <sup>46</sup> (reduced data set) <sup>b</sup>	TransATAC, R-RCT, UK	ER+, HER2– <i>n</i> = 774	LN0, 76% LN1–3, 24%	All ET, no chemotherapy	ROR-PT, nCounter	43	30.5	26.5	NR	NR	NR	NR	NR	NR	NR	0–10 years:  <ul style="list-style-type: none"> <li>Low vs. intermediate: 5.49 (2.63 to 11.48)</li> <li>Low vs. high: 12.40 (6.13 to 25.08)</li> </ul>
Gnant 2014, <sup>104</sup> Filipits 2014 <sup>105</sup>	ABCSG 8, R-RCT, Austria	ER+, HER2– <i>n</i> = 1397	LN0, 71% <sup>c</sup> LN1–3, 26% <sup>c</sup> LN> 3, 3% <sup>c</sup>	All ET, no chemotherapy	ROR-PT, nCounter	35	32	33	NR	NR	NR	96.6	91.1	79.9	5–15 years:  <ul style="list-style-type: none"> <li>Low vs. intermediate: 3.74 (NR); <i>p</i> = 0.002<sup>c</sup></li> <li>Low vs. high: 6.90 (3.08 to 15.45); <i>p</i> &lt; 0.001<sup>d</sup></li> </ul>	
Laenkhholm 2015, <sup>112</sup> 2015 <sup>113</sup>	DBCG, cohort, Denmark	HR+, HER2 NR <i>n</i> = 2722	LN0, 46% LN1–3, 54%	All ET, no chemotherapy	ROR-PT	27	29	44	NR	NR	NR	95.7	–	79.2	5–10 years:  <ul style="list-style-type: none"> <li>Low vs. intermediate: NR, <i>p</i> = 0.0074</li> <li>Intermediate vs. high: NR, <i>p</i> = 0.0091</li> </ul>	
<b>LNO</b>																
<i>100% ET monotherapy</i>																
Sestak 2017 (data request) <sup>46</sup> (full data set) <sup>b</sup>	TransATAC, R-RCT, UK	ER+, HER2– <i>n</i> = 663	LN0	All ET, no chemotherapy	ROR-PT, nCounter	55	30	15	98.6	95.9	87.9	97.4	86.6	69.0	0–5 years:  <ul style="list-style-type: none"> <li>Low vs. intermediate: 3.02 (0.99 to 9.22)</li> <li>Low vs. high: 8.87 (3.12 to 25.17)</li> </ul> 0–10 years:  <ul style="list-style-type: none"> <li>Low vs. intermediate: 5.02 (2.32 to 10.86)</li> <li>Low vs. high: 13.42 (6.33 to 28.47)</li> </ul>	

continued

TABLE 17 Prognostic performance of Prosigna: DRFS/DRFI<sup>a</sup> (continued)

Reference (first author and year)	Cohort, design, country	Population	Nodal status	ET/chemotherapy	Test	Percentage of patients per group			Percentage DRFS/DRFI risk						DMFS/DRFS: <sup>b</sup> HR (95% CI)
						Low	Intermediate	High	0–5 years			0–10 years			
									Low	Intermediate	High	Low	Intermediate	High	
Gnant 2014, <sup>104</sup> Filipits 2014 <sup>105</sup>	ABCSG 8, R-RCT, Austria	ER+, HER2– <i>n</i> = 984	LN0	All ET, no chemotherapy	ROR-PT, nCounter	48	32	20	NR	NR	NR	96.5	90.0	84.7	5–15 years: <ul style="list-style-type: none"> <li>● Low vs. intermediate: 4.03 (NR), <i>p</i> = 0.002<sup>c</sup></li> <li>● Low vs. high: 4.74 (1.89 to 11.87); <i>p</i> &lt; 0.001<sup>d</sup></li> </ul>
Laenhholm 2015 <sup>112</sup>	DBCG, cohort, Denmark	HR+, HER2 NR <i>n</i> = 1256	LN0	All ET, no chemotherapy	ROR-PT	NR	NR	NR	NR	NR	NR	95.1	92.7	81.5	0–10 years: <ul style="list-style-type: none"> <li>● Low vs. intermediate: NR, <i>p</i> = 0.1543</li> <li>● Intermediate vs. high: NR, <i>p</i> &lt; 0.0001</li> </ul>
<b>LN+</b>															
<i>100% ET monotherapy</i>															
Sestak 2017 (data request) <sup>46</sup> (full data set) <sup>b</sup>	TransATAC, R-RCT, UK	ER+, HER2– <i>n</i> = 192	LN1–3	All ET, no chemotherapy	ROR-PT, nCounter	8	32	60	100.0	91.7	87.4	100.0	80.7	70.7	0–5 years: <ul style="list-style-type: none"> <li>● Low vs. intermediate or low vs. high: no events</li> <li>● Intermediate vs. high: 1.30 (0.47 to 3.60)</li> </ul> 0–10 years: <ul style="list-style-type: none"> <li>● Low vs. intermediate or low vs. high: no events</li> <li>● Intermediate vs. high: 1.37 (0.69 to 2.72)</li> </ul>

Reference (first author and year)	Cohort, design, country	Population	Nodal status	ET/chemotherapy	Test	Percentage of patients per group			Percentage DRFS/DRFI risk						DMFS/DRFS: <sup>a</sup> HR (95% CI)
						Low	Intermediate	High	0–5 years			0–10 years			
									Low	Intermediate	High	Low	Intermediate	High	
Gnant 2014, <sup>104</sup> Filipits 2014 <sup>105</sup>	ABCSG 8, R-RCT, Austria	ER+, HER2– <i>n</i> = 413	<ul style="list-style-type: none"> <li>LN1–3, 89%<sup>c</sup></li> <li>LN &gt; 3, 11%<sup>c</sup></li> </ul>	All ET, no chemotherapy	ROR-PT, nCounter	4	34	62	NR	NR	NR	100	93.6	76.2	5–15 years: <ul style="list-style-type: none"> <li>Low vs. intermediate or low vs. high: no events</li> <li>Intermediate vs. high: 3.15 (1.20 to 8.24); <i>p</i> = 0.020<sup>d</sup></li> </ul>
Laenkhholm 2015 <sup>112</sup>	DBCG, cohort, Denmark	HR+, HER2 NR <i>n</i> = 1466	LN1–3	All ET, no chemotherapy	ROR-PT	25	27	48	NR	NR	NR	95.2		78.1	0–10 years: <ul style="list-style-type: none"> <li>Low/intermediate vs. high: NR, <i>p</i> &lt; 0.0001</li> </ul>
<i>100% chemotherapy and ET</i>															
Martin 2016, <sup>108</sup> 2014 <sup>109</sup>	GEICAM 9906, R-RCT, Spain	ER+, HER2– <i>n</i> = 536	<ul style="list-style-type: none"> <li>LN1–3, 64%</li> <li>LN &gt; 3, 36%</li> </ul>	All ET, no chemotherapy	ROR-PT (research)	19	56	26	NR	NR	NR	92	74	66	0–10 years: <ul style="list-style-type: none"> <li>Low vs. intermediate: 4.4 (NR)</li> <li>Low vs. high: 5.8 (NR), <i>p</i> &lt; 0.0001</li> </ul>

ET, endocrine therapy; NR, not reported; R-RCT, reanalysis of RCT.

a DMFS (GEICAM, ABCSG); DRFI (TransATAC).

b Full data set = all patients with EndoPredict data available; reduced data set = patients with data for all four in-scope tests analysed in TransATAC.

c Nodal status for all patients; NR for HER2– subgroup.

d 5–15 years in ABCSG 8 analysis of Prosigna.

TABLE 18 Additional prognostic value for DRFI/DRFS: Prosigna

Reference (first author and year)	Cohort	Population	Nodal status	ET/chemotherapy	Outcome	Test or comparator <sup>a</sup>	Likelihood ratio $\chi^2$	Increase in likelihood ratio $\chi^2$ over clinicopathological factors <sup>a</sup>	C-index (AUC)	Increase in C-index (AUC) over clinicopathological factors <sup>a</sup>	Multivariable model (adjutant for clinicopathological factors <sup>b</sup> ): HR (95% CI)
<b>LN status mixed</b>											
<i>100% ET monotherapy</i>											
Sestak 2017 (data request) <sup>46</sup> (reduced data set) <sup>b</sup>	TransATAC, R-RCT	ER+, HER2- <i>n</i> = 774	<ul style="list-style-type: none"> <li>LN0, 76%</li> <li>LN1-3, 24%</li> </ul>	All ET, no chemotherapy	10-year DRFI	ROR-PT, nCounter	61.47 ( <i>p</i> < 0.0001)	Over CTS: 26.30 ( <i>p</i> < 0.001)  Over NPI: 23.91 ( <i>p</i> < 0.0001)			
Gnant 2014, <sup>104</sup> Filipits 2014 <sup>105</sup>	ABCSG 8, R-RCT	ER+, HER2- <i>n</i> = 1397	<ul style="list-style-type: none"> <li>LN0, 71%<sup>c</sup></li> <li>LN1-3, 26%<sup>c</sup></li> <li>LN&gt; 3, 3%<sup>c</sup></li> </ul>	All ET, no chemotherapy	10-year DRFS	ROR-PT, nCounter		29.94 ( <i>p</i> < 0.0001)	0.720	NR	Low vs. intermediate: 2.15 (1.21 to 3.81); <i>p</i> = 0.009  Low vs. high: 4.26 (2.44 to 7.43); <i>p</i> < 0.0001
Laenkhölm 2015 <sup>112</sup>	DBCG, cohort	HR+, HER2 NR <i>n</i> = 2722	<ul style="list-style-type: none"> <li>LN0, 46%</li> <li>LN1-3, 54%</li> </ul>	All ET, no chemotherapy	10-year DRFS	ROR-PT, nCounter		<i>p</i> < 0.0001	0.688		HR (20-point change in ROR): 1.7 (1.5 to 1.9)
<b>LN0</b>											
<i>100% ET monotherapy</i>											
Sestak 2017 (data request) <sup>46</sup> (reduced data set) <sup>b</sup>	TransATAC, R-RCT	ER+, HER2- <i>n</i> = 591	LN0	All ET, no chemotherapy	10-year DRFI	ROR-PT, nCounter	50.77 ( <i>p</i> < 0.0001)	Over CTS: 23.71 ( <i>p</i> < 0.0001)  Over NPI: 25.54 ( <i>p</i> < 0.0001)			
Gnant 2014, <sup>104</sup> Filipits 2014 <sup>105</sup>	ABCSG 8, R-RCT	ER+, HER2- <i>n</i> = 984	LN0	All ET, no chemotherapy	10-year DRFS	ROR-PT, nCounter		Over CLP: 20.32 ( <i>p</i> < 0.0001)	0.692	NR	
Wallden 2015 <sup>115</sup>	British Columbia, cohort	ER+, 91%; HER2- <i>n</i> = 232	LN0	All ET, no chemotherapy	DRFS (time NR)	ROR-PT, nCounter			0.675 <sup>d</sup>	NR	
						AOL			0.587 <sup>d</sup>	NR	
						IHC-T			0.590 <sup>d</sup>	NR	

Reference (first author and year)	Cohort	Population	Nodal status	ET/chemotherapy	Outcome	Test or comparator <sup>a</sup>	Likelihood ratio $\chi^2$	Increase in likelihood ratio $\chi^2$ over clinicopathological factors <sup>a</sup>	C-index (AUC)	Increase in C-index (AUC) over clinicopathological factors <sup>a</sup>	Multivariable model (adjuvant for clinicopathological factors <sup>a</sup> ): HR (95% CI)
<b>LN+</b>											
<i>100% ET monotherapy</i>											
Sestak 2017 (data request) <sup>46</sup> (reduced data set) <sup>b</sup>	TransATAC, R-RCT, UK	ER+, HER2- <i>n</i> = 183	LN1-3	All ET, no chemotherapy	10-year DRFI	ROR-PT, nCounter	8.51 ( $p$ = 0.004)	Over CTS: 4.39 ( $p$ = 0.04)  Over NPI: 2.71 ( $p$ = 0.09)			
Gnant 2014, <sup>104</sup> Filipits 2014 <sup>105</sup>	ABCSG 8, R-RCT	ER+, HER2- <i>n</i> = 413	<ul style="list-style-type: none"> <li>LN1-3, 89%<sup>d</sup></li> <li>LN &gt; 3, 11%<sup>c</sup></li> </ul>	All ET, no chemotherapy	10-year DRFS	ROR-PT, nCounter  CLP		Over CLP: 17.45 ( $p$ = 0.0002)	0.743	NR	
Ejlertsen 2015 <sup>111</sup>	DBCG, cohort	HR+, HER2 NR <i>n</i> = 1466	LN1-3	All ET, no chemotherapy	10-year DMFS	ROR-PT, nCounter			0.667		<ul style="list-style-type: none"> <li>LN1, <math>p</math> &lt; 0.0001</li> <li>LN2, <math>p</math> = 0.0001</li> <li>LN3, <math>p</math> = 0.008</li> </ul>
<i>100% chemotherapy and ET</i>											
Martin 2016, <sup>108</sup> 2014 <sup>109</sup>	GEICAM 9906, R-RCT	ER+, HER2- <i>n</i> = 536	<ul style="list-style-type: none"> <li>LN1-3, 64%</li> <li>LN &gt; 3, 36%</li> </ul>	All ET, no chemotherapy	10-year DMFS	ROR-PT, RT-qPCR (research)			0.644	Adding ROR-PT to EPclin plus clinicopathological: $p$ = 0.567	

ET, endocrine therapy; IHC-T, IHC-4 plus tumour size; NR, not reported; R-RCT, reanalysis of RCT.

<sup>a</sup> Clinicopathological factors (ABCSG) = age, grade, nodal status, tumour size and Ki-67. Clinicopathological factors (GEICAM) = age, grade, nodal status, tumour size and treatment. ER, PR and Ki-67. CTS (TransATAC) and CLP (ABCSG 8) = age, grade, nodal status, tumour size and treatment. Clinicopathological factors (DBCG): not reported which.

<sup>b</sup> Full data set = all patients with EndoPredict data available; reduced data set = patients with data for all four in-scope tests analysed in TransATAC.

<sup>c</sup> Nodal status for all patients, NR for HER2- subgroup.

<sup>d</sup> Estimated from graph.

here. Patients received endocrine monotherapy in two trials<sup>36,46,120</sup> and all patients received endocrine therapy and chemotherapy in the GEICAM trial.<sup>108,109</sup> All excluded some original trial participants (or this was unclear). A detailed narrative synthesis of study characteristics is provided in *Report Supplementary Material 7*. This supplement also contains relevant data in tables.

### Quality assessment

The EAG's assessment of study quality is provided in *Report Supplementary Material 7, Table 2*. All analyses excluded some original trial patients (or this was unclear), sometimes owing to insufficient tumour samples, which may introduce bias owing to attrition of patients with smaller tumours. Blinding of test assessors to outcomes was reported in two analyses.<sup>36,108,109</sup> All used standardised outcomes. A discussion of how these factors might affect results is given in *Results: oncotype DX*.

### Results

A summary of key results from the review is provided in this section. A detailed narrative synthesis of all study results is provided in *Report Supplementary Material 7*.

#### *Distribution of patients by risk group*

Data are presented in *Table 19*. The percentage of LN0 patients categorised as low risk in accordance with EPclin was 73%<sup>46</sup> and the percentage categorised as high risk was 27%.<sup>46</sup> For LN+ patients,<sup>36,46,108,109</sup> the percentages categorised as low risk were 13%<sup>108,109</sup> and 24%<sup>46</sup> and the percentages categorised as high risk were 87%<sup>108,109</sup> and 76%.<sup>46</sup>

#### *Prognostic performance: unadjusted analyses*

Data are presented in *Table 19*. EPclin was a statistically significantly prognostic for DRFS/DRFI for all unadjusted analyses at 10 years (and most analyses at 5 years) in LN0 and LN+ patients<sup>46,108,109,120</sup> and in one analysis of patients at high clinical risk.<sup>120</sup> The rate of 10-year DRFS/DRFI was 94% for EPclin low-risk LN0 patients<sup>46</sup> and 95% for LN+ patients<sup>46,118–120</sup> in one study in which patients had endocrine monotherapy<sup>46</sup> and 100% in one study using endocrine therapy and chemotherapy.<sup>108,109</sup> Use of chemotherapy in the GEICAM study<sup>108,109</sup> could influence patient outcomes in either direction: negatively owing to the potential selection of higher-risk patients or positively owing to the effect of chemotherapy. The HR in LN0 patients for the low- versus high-risk groups was 3.90 (95% CI 2.33 to 6.53; *p*-value not reported) in TransATAC.<sup>46</sup> HRs in LN+ patients for the low- versus high-risk groups were 6.77 (95% CI 1.63 to 28.07; *p*-value not reported) in TransATAC,<sup>46</sup> and were not estimable for GEICAM because there were no events in the low-risk group (*p* < 0.0001).<sup>108,109</sup> *Report Supplementary Material 7* provides data comparing EPclin with clinical guidelines and a subgroup analysis of patients at high clinical risk.

#### *Additional prognostic value: adjusted analyses*

Data are presented in *Table 20*. In terms of additional prognostic value, TransATAC reported statistically significant increases in likelihood ratio  $\chi^2$  for 10-year DRFI for EPclin plus CTS/NPI over CTS/NPI only, in both LN0 and LN+ patients [LN0 patients 15.22 (*p* < 0.0001) over CTS and 17.00 (*p* < 0.0001) over NPI; LN+ patients 7.36 (*p* = 0.007) over CTS and 5.57 (*p* = 0.02) over NPI].<sup>46</sup> Two further studies reported that the EndoPredict score added statistically significant information over clinicopathological variables in LN+ and mixed LN0/LN+ patients [based on multivariable analyses and differences in C-index (AUC) for 10-year DMFS/DRFI]; however, neither study reported the additional prognostic value of EPclin.<sup>108,109,118–120</sup>

### Conclusions: EndoPredict and EndoPredict Clinical prognostic performance

Based on three reanalyses of RCTs (total *n* = 3135) in ER+, HER2-, endocrine-treated patients, EPclin was statistically significantly prognostic for unadjusted analyses of 10-year DRFS/DRFI in LN0 and LN+ patients. The percentage of patients categorised as EPclin low risk was 73% for LN0 patients and was 13% and 24% for LN+ patients. The 10-year DRFS/DRFI rates for low-risk patients were approximately 95% in LN0 and LN+ patients receiving endocrine therapy only. EPclin added statistically significant information over CTS/NPI in LN0 and LN+ patients in TransATAC, and in two further studies the EndoPredict score added statistically significant information over clinicopathological variables in mixed LN0/LN+ and LN+ patients

TABLE 19 Prognostic performance of EndoPredict and EPclin: DRFS/DRFI<sup>a</sup>

Reference (first author and year)	Cohort, design, country	Population	Nodal status	ET/chemotherapy	Test or comparator	Percentage of patients per group		Percentage DRFS/DRFI risk				DMFS/DRFS/DRFI: <sup>a</sup> HR (95% CI)
						Low	High	0–5 years		0–10 years		
<b>Reanalyses of RCTs: LN status mixed</b>												
<i>100% ET monotherapy</i>												
Sestak 2017 (data request) <sup>46</sup> (reduced data set) <sup>b</sup>	TransATAC, R-RCT, UK	ER+, HER2– <i>n</i> = 774	<ul style="list-style-type: none"> <li>LN0, 76%</li> <li>LN1–3, 24%</li> </ul>	All ET, no chemotherapy	EPclin	61	39	NR	NR	NR	NR	0–10 years: 4.65 (2.98 to 7.24)
Dubsky 2013, <sup>120</sup> 2013 <sup>119</sup>	ABCSG-6 plus ABCSG 8, R-RCT, Austria	ER+, HER2– <i>n</i> = 1702	<ul style="list-style-type: none"> <li>LN0, 68%</li> <li>LN1–3, 27%</li> <li>LN &gt; 3, 5%</li> </ul>	All ET, no chemotherapy	EndoPredict	49	51	NR	NR	NR	NR	<ul style="list-style-type: none"> <li>0–5 years: 2.80 (1.81 to 4.34); <i>p</i> &lt; 0.001</li> <li>5–10 years: 3.28 (1.48 to 7.24); <i>p</i> = 0.002</li> </ul>
					EPclin	63	37	NR	NR	95.3	NR	<ul style="list-style-type: none"> <li>0–5 years: 4.82 (3.12 to 7.44); <i>p</i> &lt; 0.001</li> <li>0–10 years: 5.11 (3.48 to 7.51); <i>p</i> &lt; 0.001</li> <li>5–10 years: 6.25 (2.72 to 14.36); <i>p</i> &lt; 0.001</li> </ul>
<b>Reanalyses of RCTs: LN0</b>												
<i>100% ET monotherapy</i>												
Sestak 2017 (data request) <sup>46</sup> (full data set) <sup>b</sup>	TransATAC, R-RCT, UK	ER+, HER2– <i>n</i> = 680	LN0	All ET, no chemotherapy	EPclin	73	27	97.9	92.2	94.1	80.0	<ul style="list-style-type: none"> <li>0–5 years: 3.91 (1.73 to 8.79)</li> <li>0–10 years: 3.90 (2.33 to 6.53)</li> </ul>
<b>Reanalyses of RCTs: LN+</b>												
<i>100% ET monotherapy</i>												
Sestak 2017 (data request) <sup>46</sup> (full data set) <sup>b</sup>	TransATAC, R-RCT, UK	ER+, HER2– <i>n</i> = 198	LN1–3	All ET, no chemotherapy	EPclin	24	76	97.9	87.6	95.0	71.6	<ul style="list-style-type: none"> <li>0–5 years: 6.00 (0.80 to 44.93)</li> <li>0–10 years: 6.77 (1.63 to 28.07)</li> </ul>
<i>100% chemotherapy and ET</i>												
Martin 2016, <sup>108</sup> 2014 <sup>109</sup>	GEICAM 9906, R-RCT, Spain	ER+, HER2– <i>n</i> = 555	<ul style="list-style-type: none"> <li>LN1–3, 64%</li> <li>LN &gt; 3, 36%</li> </ul>	All ET, no chemotherapy	EndoPredict	25	75	NR	NR	93	70	0–10 years: 4.8, (2.5 to 9.6); <i>p</i> < 0.0001
					EPclin	13	87	NR	NR	100	72	0–10 years: not estimable, <i>p</i> < 0.0001
		Premenopausal, <i>n</i> = 300	NR	<ul style="list-style-type: none"> <li>LN1–3, 64%</li> <li>LN &gt; 3, 36%</li> </ul>	EndoPredict	24	76			93	67	0–10 years: 6.7 (2.4 to 18.3); <i>p</i> < 0.0001
		Postmenopausal, <i>n</i> = 255	NR		EndoPredict	27	73			92	74	0–10 years: 3.3 (1.3 to 8.5); <i>p</i> = 0.0069
		Premenopausal, <i>n</i> = 300	NR	<ul style="list-style-type: none"> <li>LN1–3, 64%</li> <li>LN &gt; 3, 36%</li> </ul>	EPclin	12	88			100	70	0–10 years: HR NR, <i>p</i> = 0.0006
	Postmenopausal, <i>n</i> = 255	NR		EPclin	13	87			100	76	0–10 years: HR NR, <i>p</i> = 0.0023	

continued

**TABLE 19** Prognostic performance of EndoPredict and EPclin: DRFS/DRFI<sup>a</sup> (continued)

Reference (first author and year)	Cohort, design, country	Population	Nodal status	ET/chemotherapy	Test or comparator	Percentage of patients per group		Percentage DRFS/DRFI risk				DMFS/DRFS/DRFI: <sup>a</sup> HR (95% CI)
						Low	High	0–5 years		0–10 years		
<b>High/intermediate risk via clinical guidelines (LN0/LN+)</b>												
Dubsky 2013 <sup>120</sup>	ABCSG-6 plus ABCSG 8, R-RCT, Austria	NCCN, n = 1603	LN+/LN0 (% NR)	All ET, no chemotherapy	EPclin	61	39	NR	NR	95	77	0–10 years: 5.09 (3.42 to 7.58); p < 0.001
		St Gallen, n = 1358			EPclin	58	42	NR	NR	95	75	0–10 years: 5.18 (3.38 to 7.93); p < 0.001
		S3 <sup>c</sup> , n = 1454			EPclin	58	42	NR	NR	95	76	0–10 years: 5.60 (3.64 to 8.61); p < 0.001

ET, endocrine therapy; NR, not reported; R-RCT, reanalysis of RCT.  
a DMFS (GEICAM, ABCSG for ROR-PT); DRFI (TransATAC); DRFI (ABCSG for EPclin).  
b Full data set = all patients with EndoPredict data available; reduced data set = patients with data for all four in-scope tests analysed in TransATAC.  
c German S3 guideline 2008.

TABLE 20 Additional prognostic value for DRFI/DMFS: EndoPredict and EPclin

Reference (first author and year)	Cohort, design, country	Population	Nodal status	ET/chemotherapy	Outcome	Test or comparator <sup>a</sup>	Likelihood ratio $\chi^2$	Increase in likelihood ratio $\chi^2$ over clinicopathological factors	C-index (AUC)	Increase in C-index (AUC) over clinicopathological factors <sup>a</sup>	Multivariable model (adjuvant for clinicopathological factors <sup>b</sup> ): HR (95% CI)
<b>Reanalyses of RCTs: LN status mixed</b>											
<i>100% ET monotherapy</i>											
Sestak 2017 (data request) <sup>46</sup> (reduced data set) <sup>b</sup>	TransATAC, R-RCT, UK	ER+, HER2- n = 774	<ul style="list-style-type: none"> <li>LN0, 76%</li> <li>LN1-3, 24%</li> </ul>	All ET, no chemotherapy	10-year DRFI	EPclin	69.31 ( $p < 0.0001$ )	<ul style="list-style-type: none"> <li>Over CTS: 24.39 (<math>p &lt; 0.0001</math>)</li> <li>Over NPI: 22.17 (<math>p &lt; 0.0001</math>)</li> </ul>			
Dubsky 2013, <sup>120</sup> 2013 <sup>119</sup>	ABCSG 6 plus ABCSG 8, R-RCT, Austria	ER+, HER2- n = 1702	<ul style="list-style-type: none"> <li>LN0, 68%</li> <li>LN1-3, 27%</li> <li>LN &gt; 3, 5%</li> </ul>	All ET, no chemotherapy	0- to 5-year DMFS	EndoPredict					1.20 (1.10 to 1.31); $p < 0.001$
					5- to 10-year DMFS	EndoPredict					1.28 (1.10 to 1.48); $p = 0.001$
						EPclin			0.786		
						EndoPredict vs. AOL			0.765	$p < 0.001$	
						EndoPredict vs. clinicopathological <sup>a</sup>			0.716	$p < 0.001$	
	AOL			0.674							
	Clinicopathological factors <sup>a</sup>			0.644							
<b>Reanalyses of RCTs: LN0</b>											
<i>100% ET monotherapy</i>											
Sestak 2017 (data request) <sup>46</sup> (reduced data set) <sup>b</sup>	TransATAC, R-RCT, UK	ER+, HER2- n = 591	LN0	All ET, no chemotherapy	5-year DRFI	EPclin	16.62 ( $p < 0.0001$ )	<ul style="list-style-type: none"> <li>Over CTS: 5.11 (<math>p = 0.02</math>)</li> <li>Over NPI: 5.73 (<math>p = 0.02</math>)</li> </ul>			
					10-year DRFI		40.60 ( $p < 0.0001$ )	<ul style="list-style-type: none"> <li>Over CTS: 15.22 (<math>p &lt; 0.0001</math>)</li> <li>Over NPI: 17.00 (<math>p &lt; 0.0001</math>)</li> </ul>			

continued

**TABLE 20** Additional prognostic value for DRFI/DMFS: EndoPredict and EPclin (*continued*)

Reference (first author and year)	Cohort, design, country	Population	Nodal status	ET/chemotherapy	Outcome	Test or comparator <sup>a</sup>	Likelihood ratio $\chi^2$	Increase in likelihood ratio $\chi^2$ over clinicopathological factors	C-index (AUC)	Increase in C-index (AUC) over clinicopathological factors <sup>a</sup>	Multivariable model (adjuvant for clinicopathological factors <sup>b</sup> ): HR (95% CI)
<b>Reanalyses of RCTs: LN+</b>											
<i>100% ET monotherapy</i>											
Sestak 2017 (data request) <sup>46</sup> (reduced data set) <sup>b</sup>	TransATAC, R-RCT, UK	ER+, HER2- <i>n</i> = 183	LN1-3	All ET, no chemotherapy	5-year DRFI	EPclin	4.24 ( <i>p</i> < 0.039)	<ul style="list-style-type: none"> <li>Over CTS: 1.86 (<i>p</i> = 0.20)</li> <li>Over NPI: 1.43 (<i>p</i> = 0.20)</li> </ul>			
					10-year DRFI		12.91 ( <i>p</i> < 0.001)	<ul style="list-style-type: none"> <li>Over CTS: 7.36 (<i>p</i> = 0.007)</li> <li>Over NPI: 5.57 (<i>p</i> = 0.02)</li> </ul>			
<i>100% chemotherapy and ET</i>											
Martin 2016, <sup>108</sup> 2014 <sup>109</sup>	GEICAM 9906, R-RCT, Spain	ER+, HER2- <i>n</i> = 536	<ul style="list-style-type: none"> <li>LN1-3, 64%</li> <li>LN &gt; 3, 36%</li> </ul>	All ET, all chemotherapy	10-year DMFS	EPclin			0.693	NR	
						EndoPredict vs. clinicopathological <sup>a</sup>			0.672	<i>p</i> = 0.0018	
						EndoPredict			0.657		1.1 (1.0 to 1.2); <i>p</i> = 0.003
						Clinicopathological factors <sup>a</sup>			0.654		
ET, endocrine therapy; NR, not reported; R-RCT, reanalysis of RCT.											
<sup>a</sup> Clinicopathological factors (ABSCG) = age, grade, nodal status, tumour size, Ki-67; clinicopathological factors (GEICAM) = age, grade, nodal status, tumour size, treatment, ER, PR, Ki-67.											
<sup>b</sup> Full data set = all patients with EndoPredict data available; reduced data set = patients with data for all four in-scope tests analysed in TransATAC.											

(no data for EPclin). There was no evidence relating to chemotherapy benefit or clinical utility for EndoPredict or EPclin.

## Results: IHC4

### Development and analytic validity: IHC4

A narrative synthesis and data tables relating to the development of IHC4 and IHC4+C are provided in *Report Supplementary Material 8*. Although derivation data sets were excluded from the review for the other tests, for IHC4 the derivation was conducted in the TransATAC data set and is included in our tables to facilitate comparisons between tests. It should be noted, however, that estimates from TransATAC for IHC4 are likely to be an overestimate of true prognostic performance owing to overfitting.

### Analytic validity

A rapid review of the analytic validity of IHC4 can be found in *Report Supplementary Material 8*.

### Prognostic performance: IHC4 and IHC4+C

Eleven separate validation cohorts<sup>24,25,58,73,74,77,122–129</sup> have reported prognostic performance data for IHC4, with a total of 13,434 patients.

### Study designs, patients and treatments: IHC4 prognostic performance

Five cohorts [Tamoxifen vs Exemestane Adjuvant Multinational (TEAM), the WSG PlanB, Intergroup Exemestane Study (IES), GEICAM 9906 and West German Study Group epirubicine and cyclophosphamide-Doc (WSG-AGO-Doc)]<sup>24,73,74,77,122,123,126,127,129</sup> were reanalyses of RCT data (three LN+/LN0 studies,  $n = 8496$ ; no LN0 studies; two LN+ studies,  $n = 1705$ ) and six<sup>25,58,124–126,128</sup> were reanalyses of routinely collected data when patients were treated in accordance with usual practice without the use of IHC4 or IHC4+C (five LN+/LN0 studies,  $n = 3128$ ; one LN0 study,  $n = 105$ ; no LN+ studies). All studies recruited HR+ or ER+ patients except the IES RCT<sup>127</sup> and the study from Taiwan.<sup>124</sup> TransATAC,<sup>46</sup> WSG PlanB,<sup>73,74,77</sup> GEICAM 9906,<sup>129</sup> WSG-AGO-Doc,<sup>123</sup> the Kaiser Permanente cohort,<sup>125</sup> the Institut Curie<sup>128</sup> cohort and the Chinese<sup>58</sup> cohort all recruited or reported a subgroup of HER2– patients. Only one validation cohort (Stephen *et al.*<sup>126</sup>) treated 100% of patients with endocrine monotherapy, and the remainder treated varying proportions of patients with endocrine therapy and chemotherapy. Two observational studies were from East Asia;<sup>58,124</sup> clinical advice received by the EAG suggests that these two East Asian studies may be less generalisable to the English context because (1) patients were treated in accordance with usual clinical practice and this may differ between these countries and England enough to affect prognostic outcomes and (2) it is possible that people of different ethnicities have different underlying risk profiles and disease natural histories.

A detailed narrative synthesis of patient characteristics and treatments is provided in *Report Supplementary Material 8*. Overall, only the derivation cohort (TransATAC)<sup>46</sup> reported an analysis of 100% ER+, HER2–, LN0–3 patients who had not undergone chemotherapy but had received 5 years of endocrine therapy. For this reason, most of the evidence base has low generalisability to the decision problem.

### IHC4 methodology and cut-off points: IHC4 and IHC4+C prognostic performance

The methodology for conducting IHC4 is not standardised outside the Royal Marsden Hospital. *Report Supplementary Material 8* details the methods reported in the included studies, and a judgement provided by personal communication with the IHC4 methodologists [Andrew Dodson, National External Quality Assessment Service (UK), personal communication, September 2017] regarding whether or not the methods used are compatible with their own method is provided in *Report Supplementary Material 8* and *Table 21*. Seven data sets were analysed using IHC4 methodologies that were the same as or very similar to the IHC4 team's own methodology (referred to from here on in as the 'standard IHC4 methodology') [TransATAC,<sup>46</sup> TEAM,<sup>24,122,126</sup> the Nottingham cohort,<sup>25</sup> the Edinburgh Breast Conservation Series (BCS) cohort,<sup>126</sup> the Institut Curie<sup>128</sup> cohort, GEICAM 9906<sup>129</sup> and WSG-AGO-Doc<sup>123</sup>], whereas the remaining five data sets were analysed using methodologies that were unclear or dissimilar to the IHC4 team's methods

TABLE 21 Characteristics of prognostic studies: IHC4 and IHC4+C

Reference (first author and year)	Cohorts (country)	Study design	Details of test <sup>a</sup>	Compatibility <sup>b</sup> and algorithm	Population	Nodal status	ET/chemotherapy
<b>Subgroup, relevant to the decision problem, of derivation cohort: LN0/LN+</b>							
TransATAC, Sestak <sup>46</sup> <i>n</i> = 1005 <sup>c</sup>	TransATAC (UK)	R-RCT	FFPE. Biomarker expression was measured by IHC. <i>HER2</i> was confirmed by FISH if $\geq$ IHC2+. ER used 6F11 antibody (Vector Laboratories, Burlingame, CA, USA), PgR used diluted 1 : 40, clone 16 (Vector Laboratories) and Ki-67 used the diluted 1 : 100, or SP6 antibody (Abcam, Cambridge, MA, USA) diluted 1 : 100. ER positive if H > 1; PR scored as % positive cells; <i>HER2</i> by manufacturer's instructions; Ki-67 using Ariol image system (Genetix, San Jose, CA, USA)  Similar methods and scoring algorithms were used for the Nottingham cohort, except that the MiB1 antibody was used on whole sections for Ki-67, and TMAs were used for ER, PgR and <i>HER2</i>	<ul style="list-style-type: none"> <li>Compatible</li> <li>IHC4, IHC4+C</li> <li>Cuzick <i>et al.</i> 2011<sup>25</sup></li> </ul>	<ul style="list-style-type: none"> <li>100% ER+</li> <li>100% HER2–</li> <li>Postmenopausal</li> </ul>	<ul style="list-style-type: none"> <li>LN0 78.8%</li> <li>LN1–3 21.2%</li> </ul>	100% ET monotherapy
<b>Validation cohorts: LN0/LN+</b>							
Bartlett 2016 <sup>24</sup> ( <i>n</i> = 2919)	TEAM (UK/Ireland, the Netherlands, Belgium, Germany, Greece)	R-RCT	FFPE samples	<ul style="list-style-type: none"> <li>Compatible</li> <li>IHC4</li> <li>Cuzick <i>et al.</i> 2011<sup>25</sup></li> </ul>	<ul style="list-style-type: none"> <li>100% HR+</li> <li>% HER2– NR</li> <li>100% postmenopausal</li> <li>% female NR</li> </ul>	LN0/+, % NR	100% ET, some chemotherapy, % NR <sup>130</sup>
Christiansen 2012 <sup>122</sup> ( <i>n</i> = 4598)			Ariol SL50 image platform				
	Staining as per Bartlett <i>et al.</i> 2011 <sup>130</sup>  Scoring as per Faratian <i>et al.</i> 2007 <sup>131</sup>  Scores normalised						
Cuzick 2011 <sup>25</sup> <i>n</i> = 786	Nottingham (UK)	R-RD	As TransATAC <sup>46</sup>	<ul style="list-style-type: none"> <li>Compatible</li> <li>As TransATAC<sup>46</sup></li> </ul>	<ul style="list-style-type: none"> <li>100% HR+</li> <li>95% HER2–</li> <li>Premenopausal/postmenopausal</li> </ul>	<ul style="list-style-type: none"> <li>LN0 62%</li> <li>LN+ 38%</li> <li>(% LN &gt; 3 NR)</li> </ul>	52% ET, % chemotherapy NR
Nitz 2017, <sup>77</sup> Gluz 2016, <sup>73</sup> Gluz 2016 <sup>74</sup> <i>n</i> = 2642  55-month follow-up	WSG PlanB (Germany)	R-RCT	Tissue microarrays (1.4-mm diameter): ER [Rabbit (SP1)], PR (mouse monoclonal PgR636) and Ki-67 (clone 30–9 rabbit monoclonal). ER and PR positive if $\geq$ 1% stained. Ki-67 scored by one expert, > 100 cells, semi-quantitatively and quantitatively. FISH for <i>HER2</i> (unclear if confirmatory). Instead of H-score a modified score was used as described in Prat <i>et al.</i> 2013 <sup>129</sup>	<ul style="list-style-type: none"> <li>Incompatible</li> <li>IHC4</li> <li>Prat <i>et al.</i> 2013<sup>129</sup></li> <li>Cuzick <i>et al.</i> 2011<sup>25</sup></li> </ul>	<ul style="list-style-type: none"> <li>100% HR+</li> <li>100% HER2–</li> <li>Premenopausal/postmenopausal</li> <li>100% female</li> <li>High clinical risk<sup>d</sup></li> </ul>	<ul style="list-style-type: none"> <li>LN0–3</li> <li>LN0 58.8%</li> <li>LN1–3 41.2%</li> </ul>	RS < 12 ET only; RS $\geq$ 12, chemotherapy plus ET <sup>e</sup>

Reference (first author and year)	Cohorts (country)	Study design	Details of test <sup>a</sup>	Compatibility <sup>b</sup> and algorithm	Population	Nodal status	ET/chemotherapy
Rohan, 2014 <sup>125</sup> <i>n</i> = 295 (147 cases; 148 controls) <sup>f</sup>	Kaiser Permanente Northwest (USA)	CC, R-RD	FFPE samples ER, PR and <i>HER2</i> in accordance with ASCO-CAP. <sup>132,133</sup> <i>HER2</i> defined as $\geq 3$	<ul style="list-style-type: none"> <li>Unclear/unlikely</li> <li>IHC4 – UC if +C</li> <li>Cuzick <i>et al.</i> 2011<sup>25</sup></li> </ul>	<ul style="list-style-type: none"> <li>100% ER+</li> <li>100% HER2–</li> <li>Menopausal status NR</li> <li>100% female</li> </ul>	Any LN, % NR (for ER+/HER2– subgroup)	Some ET and chemotherapy, % NR (for ER+/HER2– subgroup)
Stephen, 2014 <sup>126</sup>	a) BCS	a) Cohort	FFPE	<ul style="list-style-type: none"> <li>Similar</li> <li>IHC4 (personal communication)</li> <li>Cuzick <i>et al.</i> 2011<sup>25</sup></li> </ul>	<ul style="list-style-type: none"> <li>100% ER+</li> <li>% HER2– NR</li> <li>a) % menopausal status NR</li> <li>b) 100% postmenopausal</li> <li>% female NR</li> </ul>	<ul style="list-style-type: none"> <li>LN0/LN+, % NR</li> <li>Subgroups: LN0, LN+</li> </ul>	100% ET monotherapy
a) BCS <i>n</i> = 831	b) TEAM	b) R-RCT	a) 0.6-mm <sup>2</sup> TMA cores. Dual scoring by experts <sup>134</sup>				
b) TEAM <i>n</i> = 2513	(UK/Ireland, the Netherlands, Belgium, Germany, Greece)		b) As Bartlett 2016 <sup>24</sup>				
Viale 2013 <sup>127</sup>	IES <sup>135</sup> (37 countries)	R-RCT	FFPE samples. Biomarker expression was measured by IHC. <i>HER2</i> was confirmed by FISH if $\geq$ IHC2+. Tumours were deemed positive for ER/PR if IHC $\geq 1\%$ or Allred $\geq 3$ and for <i>HER2</i> if IHC3+ or if FISH amplified. Ki-67 was high if $> 11\%$ LI (median)	<ul style="list-style-type: none"> <li>Unclear</li> <li>NR</li> </ul>	<ul style="list-style-type: none"> <li>% ER+ NR</li> <li>% HER2– NR</li> <li>100% postmenopausal</li> <li>100% female</li> </ul>	<ul style="list-style-type: none"> <li>LN NR</li> <li>(Source study recruited any LN status)<sup>135</sup></li> </ul>	100% ET, 19% chemotherapy
<i>n</i> = 1256							
<b>Validation cohorts: LN0</b>							
Vincent-Salomon, 2013 <sup>128</sup> <i>n</i> = 105	Institut Curie (France)	R-RD	FFPE. For each antibody, internal and external controls were included	<ul style="list-style-type: none"> <li>Compatible</li> <li>IHC3 – UC if +C</li> <li>Cuzick <i>et al.</i> 2011<sup>25</sup></li> <li>Used IHC3 algorithm as patients HER2–</li> </ul>	<ul style="list-style-type: none"> <li>100% ER+</li> <li>100% HER2–</li> <li>&lt; 3 cm</li> <li>Luminal BC</li> </ul>	LN0 100%	9.5% ET, 0% chemotherapy
<b>Validation cohorts: LN+</b>							
Prat, 2013 <sup>129</sup>	GEICAM 9906 <sup>136</sup> (Spain)	R-RCT	Sections air-dried overnight. General intensity score instead of H-score for ER expression <sup>129</sup>	<ul style="list-style-type: none"> <li>Compatible</li> <li>IHC4 – UC if +C</li> <li>Cuzick <i>et al.</i> 2011<sup>25</sup></li> </ul>	<ul style="list-style-type: none"> <li>100% ER+</li> <li>100% HER2–</li> <li>45% postmenopausal</li> </ul>	<ul style="list-style-type: none"> <li>100% LN+</li> <li>% LN <math>&gt; 3</math>NR (37.5% LN <math>&gt; 3</math> for unselected cohort, <i>n</i> = 1246)</li> </ul>	ET if HER2–, 100% chemotherapy
<i>n</i> = 1246							
Gluz 2016 <sup>123</sup>	WSG-AGO-Doc <sup>137</sup> (Germany)	R-RCT	Paraffin-embedded tumour blocks, no further details	<ul style="list-style-type: none"> <li>Similar, lacks granularity</li> <li>IHC4 – UC if +C</li> <li>Prat <i>et al.</i> 2013<sup>129</sup></li> <li>Cuzick <i>et al.</i> 2011<sup>25</sup></li> </ul>	<ul style="list-style-type: none"> <li>100% HR+</li> <li>100% HER2–</li> <li>Menopause NR</li> <li>% female NR</li> </ul>	LN1–3	ET in accordance with clinical guidelines, <sup>138</sup> 100% chemotherapy
<i>n</i> = 459							

continued

**TABLE 21** Characteristics of prognostic studies: IHC4 and IHC4+C (*continued*)

Reference (first author and year)	Cohorts (country)	Study design	Details of test <sup>a</sup>	Compatibility <sup>b</sup> and algorithm	Population	Nodal status	ET/chemotherapy
<b>Retrospective studies: uncertain generalisability to UK context</b>							
Gong 2016 <sup>58</sup> <i>n</i> = 611	SYSMH; CCSYU; 3rd HNC (China)	R-RD	FFPE  Scores normalised. Other details as per Cuzick <i>et al.</i> 2011. <sup>130</sup> FISH to confirm <i>HER2</i> if $\geq$ IHC2+	<ul style="list-style-type: none"> <li>Unclear</li> <li>IHC4</li> <li>Cuzick <i>et al.</i> 2011<sup>25</sup></li> </ul>	100% HR+  100% HER2–  61% postmenopausal  % female NR  non-metastatic	<ul style="list-style-type: none"> <li>LN0 46.6%</li> <li>LN+ 53.4% (% LN &gt; 3 NR)</li> </ul>	100% ET, 76.8% chemotherapy
Lin 2015 <sup>124</sup> <i>n</i> = 605	National Taiwan University Hospital (Taiwan)	R-RD	FFPE samples.  Different IHC methodologies used, used percentiles to account for differences to Cuzick <i>et al.</i> 2011. <sup>25</sup> FISH to confirm <i>HER2</i> if $\geq$ IHC2+	<ul style="list-style-type: none"> <li>Unclear/unlikely</li> <li>IHC4</li> <li>Cuzick <i>et al.</i> 2011<sup>25</sup></li> </ul>	HR+ NR  76.2% HER2–  Menopausal status NR  Female NR	Any LN, % NR	ET NR, 74.6% chemotherapy

3rd HNC, Third Hospital of Nanchang City; CC, case-control study; ET, endocrine therapy; FFPE, formalin fixed, paraffin embedded; FISH, fluorescence in situ hybridisation; GEICAM, Grupo Espanol de Investigacion en Cancer de Mama; NR, not reported; R-RCT, retrospective analysis of RCT; R-RD, retrospective analysis of routine data; RS, recurrence score; SYSMH, Sun Yat-sen Memorial Hospital; TEAM, Tamoxifen versus Exemestane Adjuvant Multicentre trial.

a Full details provided in *Report Supplementary Material 8*.

b Compatibility of test methodology to developer's methodology – further details in *Report Supplementary Material 8*.

c Data relating to the TransATAC study are also available in multiple publications, namely Sestak *et al.* 2016,<sup>39</sup> Sestak *et al.* 2013,<sup>41</sup> Sgroi *et al.* 2013<sup>43</sup> and Dowsett *et al.* 2013,<sup>38</sup> all reporting slightly different analyses. The total analysed cohort was *n* = 1125 patients. We have only extracted data relating to the cohorts of interest to the assessment provided by the TransATAC team (ER+, HER2–, LN0–3, *n* = 1048), and a further reduced data set of patients who had undergone four of the tests relevant to the decision problem (oncotype DX, IHC4, Prosigna and EPclin), *n* = 774 in total, LN0 = 591, LN+ = 183.

d HER2–; pT1-T4c; LN+ [or LN0 with a risk factor (CpT2, grade 2/3, high uPA/PAI-1, < 35 years, or HR-negative)].<sup>77</sup>

e Patients were treated in accordance with oncotype DX score, with those with a RS of < 12 receiving ET only, and those with a RS of  $\geq$  12 receiving chemotherapy plus ET.

f Controls could be matched to more than one case.

(WSG PlanB,<sup>73,74,77</sup> the Kaiser Permanente cohort,<sup>125</sup> IES,<sup>127</sup> the Chinese cohort<sup>58</sup> and the Taiwanese cohort<sup>124</sup>). Results have not been excluded by IHC4 methodology, as methodologies are not currently standardised and, for this reason, all data are of some relevance.

Data definitely stated to relate to IHC4+C were only available for the Nottingham cohort<sup>25</sup> and TransATAC.<sup>46</sup> For three studies, it was unclear whether the IHC4 score or the IHC4+C score was used. Other studies used IHC4 (TEAM analyses by Barlett *et al.*<sup>24</sup> and Stephen *et al.*,<sup>126</sup> the Edinburgh cohort,<sup>126</sup> WSG PlanB,<sup>73,74,77</sup> GEICAM 9906,<sup>129</sup> the Kaiser Permanente cohort,<sup>125</sup> the China cohort<sup>58</sup> and the Taiwan cohort).<sup>124</sup> See *Report Supplementary Material 8* and *Table 21* for a description of which cut-off points were used that included using tertiles and/or quartiles, using < 10%, 10–20% and > 20% ROR or using the score as a continuous variable.

### Quality assessment: IHC4 and IHC4+C prognostic performance

No study scored well on all items (see *Report Supplementary Material 8, Table 4*). A high number of studies included patients who had received chemotherapy treatment and a high number were not able to include all relevant patients owing to missing samples or insufficient tissue. Very few studies reported that they blinded test assessors.

### Results: IHC4 prognostic performance – unadjusted analyses

See *Table 22* and *Report Supplementary Material 8, Tables 5–7*. Across the studies reporting prognostic performance data from unadjusted analyses, none reported survival or recurrence outcomes per risk group. In the validation cohorts, HR analyses showed statistically significant performance when high-risk groups (defined by quartiles or tertiles) were compared with low-risk groups (when reported), whether in LN0/LN+ ( $n = 4$ ),<sup>24,73,74,77,124,127</sup> LN0-only ( $n = 3$ )<sup>58,124,125</sup> or LN+-only ( $n = 1$ )<sup>123</sup> patients, and regardless of patient spectrums and treatments received. However, analyses using continuous scores were not always statistically significant or did not report this. The use of continuous scores, quartiles and tertiles does not allow conclusions to be drawn about which cut-off points should be used in clinical practice and how these would perform.

### Additional prognostic value: IHC4

The additional prognostic value of IHC4 was analysed in six data sets<sup>24,73,74,77,123–126,129</sup> in total. Data are presented in *Table 23*. Data from the study by Stephen *et al.*<sup>126</sup> in the separate cohorts (BCS and TEAM<sup>126</sup>) indicated that IHC4 provided more prognostic information than clinicopathological variables in the LN0/LN+ mixed group, based on D-statistics but not when considering HRs, and was more informative for years 0–5 than for years 5–10. The same study reported HRs for only LN0 and LN+ subgroups adjusted for clinicopathological factors, and these were not statistically significant. WSG PlanB<sup>73,74,77</sup> reported additional value over clinicopathological factors in LN0/LN+ patients; in the Kaiser Permanente cohort,<sup>125</sup> IHC4 did not add additional prognostic value. Three further studies<sup>123,124,129</sup> reported on LN+ subgroups, two of which<sup>124,129</sup> reported statistically significant additional prognostic value of IHC4 over clinicopathological factors.

Broadly speaking, results did not appear to be influenced by the compatibility of the IHC4 methodology with the standard methodology, with both statistically significant and non-significant results being reported in both compatible and non-compatible studies.

### Results: IHC4+C prognostic performance – unadjusted analyses

Data relating to the prognostic performance of IHC4+C are presented in *Table 24*. Most information relating to IHC4+C comes from the TransATAC trial, which was the derivation cohort, in which unadjusted HRs between risk groups (using predefined cut-off points) for DRFI were statistically significant in LN0–3, LN0 and LN1–3 analyses, and similar results were seen for OS. Additional data from the Nottingham cohort<sup>25</sup> and IES<sup>127</sup> (although the description is ambiguous) are limited in nature, but support the observations in the TransATAC derivation trial. The TransATAC results suggest that IHC4+C is prognostic for DRFI, with HRs for high-risk versus low-risk groups (for different subgroups and time points) ranging from 4.73 (95% CI 2.79 to 8.03) to 11.39 (95% CI 4.05 to 32.01).

**TABLE 22** Prognostic performance of IHC4: DRFS and DRFI

Reference (first author and year)	Cohorts	Population	Nodal status	ET/chemotherapy	Percentage of patients per risk group			DRFS/DRFI: HR (95% CI) unless stated otherwise (0–5 years)
					Low	Intermediate	High	
<b>DRFS</b>								
<i>LNO, some ET and chemotherapy</i>								
Rohan 2014 <sup>125</sup> n = 295 (147 cases; 148 controls)	Kaiser Permanente Northwest	100% ER+, 100% HER2–	Any LN, % NR (for ER+/HER2– subgroup)	Some ET and chemotherapy, % NR (for ER+/HER2– subgroup)	40.7 <sup>a</sup>	51.9 <sup>a</sup>	7.5 <sup>a</sup>	OR: <ul style="list-style-type: none"> <li>Intermediate vs. low:<sup>a</sup> 1.76 (1.10 to 2.84)</li> <li>High vs. low:<sup>a</sup> 2.54 (0.97 to 6.62)</li> <li>p = 0.01</li> </ul> <p>Continuous</p> <p>OR per 10 units:</p> <ul style="list-style-type: none"> <li>1.09 (1.03 to 1.15)</li> <li>AUC: 0.62</li> </ul>
<i>Retrospective studies: uncertain generalisability to UK context LNO/LN+, some/all ET and chemotherapy</i>								
Gong 2016 <sup>58</sup> n = 611	SYSTEMH; CCSYU; 3rd HNC	100% HR+, 100% HER2–	<ul style="list-style-type: none"> <li>LNO 46.6%</li> <li>LN+ 53.4% (% LN &gt; 3 NR)</li> </ul>	100% ET, 76.8% chemotherapy	25.7	48.4	25.9	<ul style="list-style-type: none"> <li>High vs. low:<sup>b</sup> 1.454 (1.133 to 1.866); p = 0.003</li> <li>High vs. intermediate:<sup>b</sup> 1.370 (0.931 to 2.061); p = 0.11</li> <li>Intermediate vs. low:<sup>b</sup> 1.508 (0.941 to 2.418); p = 0.088</li> <li>AUC: 0.692 (0.617 to 0.767)</li> </ul>
Lin 2015 n = 605 <sup>124</sup>	National Taiwan University Hospital	HR+ NR, 76.2% HER2–	Any LN, % NR	ET NR, 74.6% chemotherapy	Used quartiles			<ul style="list-style-type: none"> <li>High vs. low:<sup>b</sup> 2.33 (1.41 to 3.85)</li> <li>Intermediate vs. low:<sup>b</sup> 1.88 (1.18 to 2.99)</li> </ul>
<b>DRFI</b>								
<i>LNO/LN+, some ET and chemotherapy</i>								
Cuzick 2011 <sup>25</sup> n = 786	Nottingham	100% HR+, 95% HER2–, premenopausal/postmenopausal	<ul style="list-style-type: none"> <li>LNO 62%</li> <li>LN+ 38% (% LN &gt; 3 NR)</li> </ul>	52% ET, % chemotherapy NR	0–25th, 26th–75th, 76th–100th			Below 25th vs. above 75th quartile: 4.1 (2.5 to 6.8)
<i>LNO, some/all ET and chemotherapy</i>								
Viale 2013 <sup>127</sup>	IES	% ER+ NR, % HER2– NR	LNO	100% ET, 19% chemotherapy	Used tertiles (not further defined)			<ul style="list-style-type: none"> <li>2nd tertile vs. 1st tertile: 1.4 (0.7 to 2.9)</li> <li>3rd tertile vs. 1st tertile: 2.3 (1.1 to 4.7)</li> <li>p = 0.04</li> </ul>
3rd HNC, Third Hospital of Nanchang City; ET, endocrine therapy; SYSTEMH, Sun Yat-sen Memorial Hospital.								
a Defined via tertiles: <ul style="list-style-type: none"> <li>low: ≤ –7.81</li> <li>intermediate: &gt; –7.81 to 88.32</li> <li>high: &gt; 88.32.</li> </ul>								
<b>Note</b>								
a DRFS definition unclear regarding whether non-cancer deaths were events or censored.								
b High defined as patient above the 75th percentile; low defined as patients below the 25th percentile; intermediate defined as patients from 25th to 75th percentiles.								

TABLE 23 Additional prognostic value, all outcomes: IHC4

Reference (author and year)	Cohorts	Population	Nodal status	ET/chemotherapy	Outcome	Test or comparator <sup>a</sup>	Likelihood ratio $\chi^2$	Increase in likelihood ratio $\chi^2$ over clinicopathological factors <sup>a</sup>	Other analyses
<b>LN0/LN+, 100% ET, 0% chemotherapy</b>									
Stephen 2014 <sup>126</sup>	a) BCS	100% ER+, % HER2– NR	LN0/+, % NR	100% ET monotherapy	DRFI	IHC4 vs. clinicopathological factors			MV model (adjuvant for clinicopathological factors <sup>b</sup> ): HR (95% CI): <sup>b</sup> <ul style="list-style-type: none"> <li>0–5 years: 1.79 (0.87 to 3.71)</li> <li>5–10 years: 1.20 (0.59 to 2.44)</li> </ul> Full follow-up: <sup>b</sup> % $R^2$ (95% CI) <ul style="list-style-type: none"> <li>IHC4: 26.3 (17.4 to 35.1); clinicopathological factors: 25.7 (16.7 to 34.6)</li> </ul> D-statistic (95% CI): <sup>c</sup> <ul style="list-style-type: none"> <li>IHC4: 1.22 (0.94 to 1.50); clinicopathological factors: 1.20 (0.92 to 1.48)</li> </ul> 5 years: <sup>b</sup> <ul style="list-style-type: none"> <li>% <math>R^2</math> (95% CI): IHC4: 39.0 (27.2 to 50.7); clinicopathological factors: 35.3 (23.3 to 47.4)</li> </ul> D-statistic (95% CI): <sup>c</sup> <ul style="list-style-type: none"> <li>IHC4: 1.63 (1.23 to 2.04); clinicopathological factors: 1.51 (1.12 to 1.91)</li> </ul> Clinicopathological plus IHC4 vs. clinicopathological: <ul style="list-style-type: none"> <li>Wald test: 6.4 (0.01); change <math>R^2</math> (%): 3.7; change D-statistic: 0.12</li> </ul>

continued

**TABLE 23** Additional prognostic value, all outcomes: IHC4 (*continued*)

Reference (author and year)	Cohorts	Population	Nodal status	ET/chemotherapy	Outcome	Test or comparator <sup>a</sup>	Likelihood ratio $\chi^2$	Increase in likelihood ratio $\chi^2$ over clinicopathological factors <sup>a</sup>	Other analyses
	b) TEAM		LN0+, % NR						<p>MV model (adjuvant for clinicopathological factors<sup>b</sup>), HR (95% CI):<sup>b</sup></p> <ul style="list-style-type: none"> <li>● 0–5 years: 1.34 (0.85 to 2.10)</li> <li>● 5–10 years: 0.89 (0.44 to 1.78)</li> </ul> <p>Full follow-up:<sup>b</sup></p> <ul style="list-style-type: none"> <li>● % <math>R^2</math> (95% CI): IHC4: 32.8 (27.0 to 38.4); clinicopathological factors: 29.5 (23.6 to 35.3)</li> </ul> <p>D-statistic (95% CI):<sup>c</sup></p> <ul style="list-style-type: none"> <li>● IHC4: 1.43 (1.24 to 1.62); clinicopathological factors: 1.33 (1.14 to 1.51)</li> </ul> <p>5 years:<sup>b</sup></p> <ul style="list-style-type: none"> <li>● % <math>R^2</math> (95% CI): IHC4: 34.9 (28.3 to 41.2); clinicopathological factors: 30.5 (23.7 to 37.0)</li> </ul> <p>D-statistic (95% CI):<sup>c</sup></p> <ul style="list-style-type: none"> <li>● IHC4: 1.50 (0.29 to 1.71); clinicopathological factors: 1.36 (1.14 to 1.57)</li> </ul> <p>Clinicopathological plus IHC4 vs. clinicopathological:</p> <ul style="list-style-type: none"> <li>● Wald test: 34.5 (&lt;0.001); change <math>R^2</math> (%): 4.4; change D-statistic: 0.14</li> </ul>

Reference (author and year)	Cohorts	Population	Nodal status	ET/chemotherapy	Outcome	Test or comparator <sup>a</sup>	Likelihood ratio $\chi^2$	Increase in likelihood ratio $\chi^2$ over clinicopathological factors <sup>a</sup>	Other analyses
<b>LN0/LN+, 100% ET, some chemotherapy (or chemotherapy NR)</b>									
Bartlett 2016, <sup>24</sup> Christiansen 2012 <sup>122</sup>	TEAM	100% HR+, % HER2– NR	LN0/LN+, % NR	100% ET, some chemotherapy, % NR <sup>130</sup>	IDFS	IHC4 vs. clinicopathological factors	170.0 <sup>24</sup>	38.5 (29%) <sup>24</sup>	8 years. MV model (adjuvant for clinicopathological factors <sup>b</sup> ). HR (95% CI): <sup>d</sup> 1.007 (1.005 to 1.009) <sup>122</sup>
<i>n</i> = 4598 <sup>122</sup>									
Nitz 2017 <sup>73,74,77</sup>	WSG PlanB	<ul style="list-style-type: none"> <li>100% HR+</li> <li>100% HER2–</li> <li>High clinical risk</li> <li>100% female</li> </ul>	<ul style="list-style-type: none"> <li>LN0–3</li> <li>LN0</li> <li>58.8%</li> <li>LN1–3</li> <li>41.2%</li> </ul>	100% ET, RS < 12 no chemotherapy; RS ≥ 12, chemotherapy	IDFS	IHC4 vs. clinicopathological factors			MV model (adjuvant for clinicopathological factors <sup>b</sup> ). HR (95% CI): 1.59 (95 CI 1.15 to 2.2); $p = 0.005^e$
<i>n</i> = 2642									
<b>LN0/LN+, some ET and chemotherapy</b>									
Rohan 2014 <sup>125</sup>	Kaiser Permanente Northwest	100% ER+, 100% HER2–	Any LN, % NR (for ER +/HER2– subgroup)	Some ET and chemotherapy, % NR (for ER+/HER2– subgroup)	DRFS <sup>f</sup>	IHC4 vs. clinicopathological factors			Follow-up year NR  OR (95% CI): <ul style="list-style-type: none"> <li>Intermediate vs. low:<sup>f</sup> 1.62 (0.94 to 2.81)</li> <li>High vs. low:<sup>f</sup> 1.61 (0.48 to 5.47)</li> <li><math>p = 0.12</math></li> <li>Continuous per 10 units: 1.06 (1.00 to 1.13)</li> </ul>
<i>n</i> = 295 (147 cases; 148 controls)									
<b>LN0, 100% ET, 0% chemotherapy</b>									
Stephen 2014 <sup>126</sup>	a) BCS	100% ER+, % HER2– NR	LN0	100% ET, 0% chemotherapy	DRFI	IHC4 vs. clinicopathological factors			MV model (adjuvant for clinicopathological factors <sup>b</sup> ). HR (95% CI): <ul style="list-style-type: none"> <li>0–5 years: 3.16 (1.03 to 9.64)</li> <li>5–10 years: 2.61 (0.88 to 7.75)</li> </ul>
a) BCS <i>n</i> = 657									
b) TEAM <i>n</i> = 1208	b) TEAM		LN0						MV model (adjuvant for clinicopathological factors <sup>b</sup> ). HR (95% CI): <ul style="list-style-type: none"> <li>0–5 years: 1.29 (0.58 to 2.90)</li> <li>5–10 years: 0.73 (0.23 to 2.31)</li> </ul>
<b>LN+, 100% ET, 0% chemotherapy</b>									
Stephen 2014 <sup>126</sup>	a) BCS	100% ER+, % HER2– NR	LN+	100% ET monotherapy	DRFI	IHC4 vs. clinicopathological factors			MV model (adjuvant for clinicopathological factors <sup>b</sup> ). HR (95% CI): <ul style="list-style-type: none"> <li>0–5 years: 1.02 (0.33 to 3.15)</li> <li>5–10 years: 0.53 (0.17 to 1.68)</li> </ul>
a) BCS <i>n</i> = 174									
b) TEAM <i>n</i> = 1296	b) TEAM		LN+						MV model (adjuvant for clinicopathological factors <sup>b</sup> ). HR (95% CI): <ul style="list-style-type: none"> <li>0–5 years: 1.39 (0.81 to 2.40)</li> <li>5–10 years: 0.98 (0.40 to 2.36)</li> </ul>

continued

**TABLE 23** Additional prognostic value, all outcomes: IHC4 (continued)

Reference (author and year)	Cohorts	Population	Nodal status	ET/chemotherapy	Outcome	Test or comparator <sup>a</sup>	Likelihood ratio $\chi^2$	Increase in likelihood ratio $\chi^2$ over clinicopathological factors <sup>a</sup>	Other analyses
<b>LN+, % ET NR, 100% chemotherapy</b>									
Gluz 2016 <sup>123</sup> <i>n</i> = NR <sup>e</sup>	WSG-AGO-Doc <sup>137</sup>	100% HR+, 100% HER2-	LN1-3	% ET NR, 100% chemotherapy	IDFS	IHC4 vs. clinicopathological factors			5 year MV model (adjuvant for clinicopathological factors <sup>f</sup> ). HR (95% CI):  • IHC4 (dichotomous) not significant in multivariable analysis (HR NR) <sup>g</sup>
<b>LN+, 100% ET, 100% chemotherapy</b>									
Prat 2013 <sup>129</sup> <i>n</i> = 580	GEICAM 9906 <sup>136</sup>	100% ER+, 100% HER2- 45% postmenopausal	100% LN+, % LN > 3 NR	100% ET, 100% chemotherapy	IDFS	IHC4 score vs. clinicopathological		Follow-up year NR  13.5; <i>p</i> < 0.05 (estimated from graph)	
<b>Retrospective studies: uncertain generalisability to UK context</b>									
<i>LNO/LN+, variable ET and chemotherapy</i>									
Lin 2015 <sup>124</sup> <i>n</i> = 605	National Taiwan University Hospital	HR+ NR, 76.2% HER2-	Any LN, % NR	ET NR, 74.6% chemotherapy	RFS				MV model (adjuvant for clinicopathological factors <sup>f</sup> ). HR (95% CI):  • High/intermediate vs. low: <sup>h</sup> 1.90 (1.32 to 2.73); <i>p</i> < 0.001

ET, endocrine therapy; GGI, genomic grade index; IDFS, invasive disease free survival; MV, multivariate; NR, not reported; RS, recurrence score.

a Adjusted for:  
 • Bartlett 2016<sup>24</sup> – grade, tumour size, age, nodal status, type of endocrine treatment (exemestane vs. exemestane plus tamoxifen), chemotherapy, radiation therapy.  
 • Stephen 2014<sup>126</sup> – age, grade, tumour size, nodal status, treatment.  
 • Gluz 2016<sup>123</sup> – central grade, genomic grade, Ki-67, molecular subtype, IHC4.  
 • Nitz 2017<sup>73,74,77</sup> – nodal status, tumour stage, local grade, central grade.  
 • Rohan 2014<sup>125</sup> – nodal status, tumour size, tumour grade, hormone therapy, age at diagnosis, duration of follow-up.  
 • Prat 2012<sup>129</sup> – treatment arm, histological grade, tumour stage, nodal status, age.

b High risk is > 20% risk in original (TransATAC) cohort; low risk is < 10% risk in original (TransATAC) cohort.

c Difference in D-statistic of  $\geq 0.1$  indicates improved prognostic separation.

d C-index reported in Christiansen 2012<sup>122</sup> poster presentation, but text was illegible.

e Personal communication with Professor Gluz, WSG, 27 August 2017.

f High/intermediate/low defined via tertiles: low,  $\leq -7.81$ ; intermediate,  $> -7.81$  to 88.32; high,  $> 88.32$ . DRFS definition unclear regarding whether non-cancer deaths were events or censored.

g Subgroup with GGI available.

h High defined as 75th percentile; low defined as 25th percentile; intermediate 25th to 75th percentile.

TABLE 24 Prognostic performance of IHC4+C: DRFI

Reference (first author and year)	Cohorts	Population	Nodal status	ET/chemotherapy	Percentage of patients per group			Percentage DRFI risk						DRFI: HR (95% CI)			
					Low	Intermediate	High	0–5 years			0–10 years			0–5 years	0–10 years		
<b>LN0/LN+, 100% ET, 0% chemotherapy</b>																	
TransATAC, Sestak <sup>46</sup>	TransATAC	100% ER+, HER2–	LN0–3 (n = 774 <sup>a</sup> )	100% ET, 0% chemotherapy	60 <sup>a</sup>	24 <sup>a</sup>	16 <sup>a</sup>										<ul style="list-style-type: none"> <li>Intermediate vs. low: 4.73 (2.79 to 8.03)<sup>b</sup></li> <li>High vs. low: 7.18 (4.20 to 12.28)<sup>b</sup></li> </ul>
n = 1005																	
<b>LN0/LN+, 52% ET, NR chemotherapy</b>																	
Cuzick 2011 <sup>25</sup>	Nottingham	<ul style="list-style-type: none"> <li>100% HR+</li> <li>95% HER2–</li> <li>Premenopausal/postmenopausal</li> </ul>	<ul style="list-style-type: none"> <li>LN0 62%</li> <li>LN+ 38%</li> <li>(% LN &gt; 3 NR)</li> </ul>	52% ET, % chemotherapy NR	Tertiles			Visual inspection of predicted vs. observed DRFI plot (Kaplan–Meier curves plus 95% CIs; see figure 5 in Cuzick <i>et al.</i> <sup>25</sup> ) showed good agreement between predicted and observed scores, although agreement appeared to decrease over time, with lines diverging after 6 years in the high-risk group (67–100%) and 8 years in the low- (0–33%) and intermediate-risk (33–66%) groups									
n = 786																	
<b>LN0, 100% ET, 0% chemotherapy</b>																	
TransATAC <sup>46</sup>	TransATAC	100% ER+, HER2–	LN0	100% ET, 0% chemotherapy	70 <sup>a</sup>	21 <sup>a</sup>	9 <sup>a</sup>	98.9	93.1	88.1	95.6	81.8	77.3	<ul style="list-style-type: none"> <li>Intermediate vs. low: 6.49 (2.40 to 17.54)<sup>b</sup></li> <li>High vs. low: 11.39 (4.05 to 32.01)<sup>b</sup></li> </ul>	<ul style="list-style-type: none"> <li>Intermediate vs. low: 4.37 (2.48 to 7.72)<sup>b</sup></li> <li>High vs. low: 6.42 (3.37 to 12.24)<sup>b</sup></li> </ul>		
n = 1005																	
<b>LN0, 100% ET, some chemotherapy</b>																	
Viale 2013 <sup>127</sup>	IES <sup>135</sup>	% ER+ NR, % HER2– NR	LN0	100% ET, 19% chemotherapy													States 'addition of clinical variable to IHC made the effect more profound'
<b>LN+, 100% ET, 0% chemotherapy</b>																	
TransATAC, Sestak <sup>46</sup>	TransATAC	100% ER+, HER2–	LN1–3	100% ET, 0% chemotherapy	28 <sup>a</sup>	34 <sup>a</sup>	38 <sup>a</sup>	98.3	90.2	85.8	96.1	75.8	67.2	<ul style="list-style-type: none"> <li>Intermediate vs. low: 5.92 (0.7 to –48.10)<sup>b</sup></li> <li>High vs. low: 8.82 (1.14 to 68.30)<sup>b</sup></li> </ul>	<ul style="list-style-type: none"> <li>Intermediate vs. low: 7.32 (1.68 to 31.85)<sup>b</sup></li> <li>High vs. low: 10.34 (2.44 to 43.89)<sup>b</sup></li> </ul>		
n = 219																	
DRFI, distant recurrence free interval; ET, endocrine therapy; NR, not reported.																	
a These analyses used a cut-off point of < 10% risk, 10–20% and > 20% risk to define low-, intermediate- and high-risk groups, respectively.																	
b These data are from the reduced data set.																	

### Additional prognostic value: IHC4+C

Data relating to the additional prognostic value of IHC4+C are presented in *Table 25*. The IHC4+C appeared to have additional prognostic value over NPI and CTS, but this was based on the derivation cohort (TransATAC), with increases in likelihood ratio  $\chi^2$  for DRFI, ranging from 17 to 26 across LN0/LN+, LN0 and LN1–3 groups, compared with CTS and NPI (increases were statistically significant for LN0 patients but not for LN+ patients). In the validation cohort (Nottingham<sup>25</sup>), the HR adjusted for clinicopathological variables remained statistically significant (HR 3.9, 95% CI 2.3 to 6.5).

### Conclusions: IHC4 and IHC4+C

The IHC4 score has been validated in five reanalyses of RCTs and six retrospective cohort studies, and provides statistically significant prognostic information consistently in unadjusted analyses in LN+/LN0, LN0 and LN+ groups. However, most studies used quartiles or tertiles to define risk groups, which does not allow conclusions to be drawn about which cut-off points should be used in clinical practice and how these would perform. Many studies used laboratory methods that differed from the derivation study methodology. Only one validation study, by Stephen *et al.*,<sup>126</sup> reports using the cut-off points from the original analysis,<sup>25</sup> which provides a second and third validation cohort (BCS and TEAM), but only for the IHC4 component of the test, not including the clinical factors component (i.e. IHC4+C). IHC4 was shown to have additional prognostic value over clinicopathological factors in some studies. Test methodologies did not appear to have an impact on the statistical significance of test results, but this does not mean that their performance is necessarily the same, and concerns remain about the conduct of the test in laboratories other than that used to derive the score. IHC4+C had prognostic value in unadjusted analyses in the derivation cohort and one validation cohort. Additional prognostic value has been reported in the derivation cohort in which IHC4+C provided statistically significantly more information than NPI in LN0 patients but not in LN+ patients, and in one validation cohort (Nottingham<sup>25</sup>) in which statistical significance was maintained after adjustments for clinicopathological factors.

## Results: all tests compared with each other

The results of all tests compared with each other can be found in *Appendix 5*, which provides an overview of three types of studies that allow some form of comparison between tests:

- Studies reporting more than one test – these are studies in which two or more of the tests were conducted and patient outcomes were reported, such that the prognostic performance of two or more tests in the same cohort can be compared. Very few studies conduct formal comparisons between tests.
- Microarray studies – these are studies in which the commercial versions of the tests were not used, but rather test algorithms were applied to genetic profiles obtained using microarray techniques. Mostly, these are publicly available in in silico (electronic database) genetic profiles, complete with patient outcome data. As with the studies that report more than one test, the comparisons provided are not always formal. There were also a number of microarray studies that reported data for one test only, which are detailed in *Report Supplementary Material 10*.
- Concordance in risk categorisation between tests – focusing on the OPTIMA Prelim study.

## Results: decision impact studies

### Decision impact: study and patient characteristics

Decision impact studies assess how decisions to use or not to use chemotherapy changed pre and post availability of the test. *Report Supplementary Material 9, Tables 1–5*, show the study characteristics of the included decision impact studies, including whether studies were prospective or retrospective and whether the data were for chemotherapy recommendations or actual treatment decisions. The ER, *HER2* and nodal statuses are also shown.

TABLE 25 Additional prognostic value, all outcomes: IHC4+C

Reference (first author and year)	Cohorts	Population	Nodal status	ET/chemotherapy	Outcome	Test or comparator	Likelihood ratio $\chi^2$	Increase in likelihood ratio $\chi^2$ over clinicopathological factors	Other analyses
<b>LN0/LN+, 100% ET, 0% chemotherapy</b>									
TransATAC <sup>46</sup> <i>n</i> = 774 (reduced data set)	TransATAC	100% ER+, HER2–	LN0–3	100% ET, 0% chemotherapy	DRFI	IHC4+C (continuous) vs. CTS  IHC4+C (continuous) vs. NPI	10 years: 75.30, <i>p</i> < 0.0001	10 years: 20.07 ( <i>p</i> < 0.0001)  10 years: 22.84 ( <i>p</i> < 0.0001)	
Cuzick 2011 <sup>25</sup> <i>n</i> = 786	Nottingham	<ul style="list-style-type: none"> <li>100% HR+</li> <li>95% HER2–</li> <li>Premenopausal/postmenopausal</li> </ul>	<ul style="list-style-type: none"> <li>LN0 62%</li> <li>LN+ 38%</li> <li>(% LN &gt; 3 NR)</li> </ul>	52% ET, % chemotherapy NR	DRFI	IHC4+C vs. clinical score	25.89, <i>p</i> < 0.0001		MV model (adjuvant for clinicopathological factors). HR (95% CI):  • 3.9 (2.3 to 6.5)
<b>LN0, 100% ET, 0% chemotherapy</b>									
TransATAC <sup>46</sup> <i>n</i> = 591 (reduced data set)	TransATAC	100% ER+, HER2–	LN0	100% ET, 0% chemotherapy	DRFI	IHC4+C (continuous) vs. CTS  IHC4+C (continuous) vs. NPI	<ul style="list-style-type: none"> <li>5 years: 30.43, <i>p</i> &lt; 0.0001</li> <li>10 years: 48.55, <i>p</i> &lt; 0.0001</li> </ul>	5 years: 18.03, <i>p</i> < 0.0001  5 years: 17.89, <i>p</i> < 0.0001	10 years: 17.14, <i>p</i> < 0.0001  10 years: 21.92, <i>p</i> < 0.0001
<b>LN+, 100% ET, 0% chemotherapy</b>									
TransATAC <sup>46</sup> <i>n</i> = 183 (reduced data set)	TransATAC	100% ER+, HER2–	LN1–3	100% ET, 0% chemotherapy	DRFI	IHC4+C (continuous) vs. CTS  IHC4+C (continuous) vs. NPI	<ul style="list-style-type: none"> <li>5 years: 7.40, <i>p</i> &lt; 0.0065</li> <li>10 years: 12.60, <i>p</i> &lt; 0.001</li> </ul>	5 years: 2.64, <i>p</i> = 0.10  5 years: 2.65, <i>p</i> = 0.10	10 years: 3.08, <i>p</i> = 0.08  10 years: 2.45, <i>p</i> = 0.10
ET, endocrine therapy; MV, multivariate; NR, not reported.									

Five UK studies<sup>139–145</sup> and 12 other European studies<sup>146–158</sup> assessed the decision impact of onco<sup>type</sup> DX (see *Report Supplementary Material 9, Table 1*); the results of one further study were provided as commercial in confidence and could not be presented here.<sup>62</sup> One UK study<sup>159</sup> and three other European studies<sup>160–162</sup> assessed the decision impact of EndoPredict (EP<sup>Cl</sup>in) (see *Report Supplementary Material 9, Table 2*). One UK study<sup>163</sup> and no other European studies assessed the decision impact of IHC4+C (see *Report Supplementary Material 9, Table 3*). No UK studies and three other European studies<sup>164–166</sup> assessed the decision impact of Prosigna (see *Report Supplementary Material 9, Table 4*). No UK studies and eight European studies<sup>81,167–173</sup> assessed the decision impact of MammaPrint (see *Report Supplementary Material 9, Table 5*).<sup>62</sup>

### Decision impact: results

In most studies, patients were allocated pre test to either chemotherapy or no chemotherapy. This could be a recommendation (by a physician or multidisciplinary team) or an actual treatment decision (what the patient actually received). They were then split into four post-test groups: those whose decision/recommendation (1) remained chemotherapy, (2) remained no chemotherapy, (3) changed from no chemotherapy to chemotherapy or (4) changed from chemotherapy to no chemotherapy. *Tables 26–30* provide these data. These data are also summarised in terms of the proportion of patients undergoing any treatment change (either to or from chemotherapy), the total proportion allocated to chemotherapy both pre and post test and the net change in chemotherapy use. Within each results table subheading, studies are broadly ordered as LN0, then mixed nodal status and then LN+.

### Oncotype DX

Among four UK studies,<sup>139–144</sup> the percentage of patients with any change in treatment recommendation or decision (either to or from chemotherapy) ranged from 29% to 49% (*Table 26*). Across 11 European (non-UK) studies,<sup>146–157</sup> the percentage of patients with any change in treatment recommendation or decision ranged from 5% to 70%. There was little clear difference in results in accordance with LN status.

Among UK studies, the net reduction in chemotherapy recommendations (pre test to post test) was 14% to 23% across two studies,<sup>143,144</sup> and the net reduction in chemotherapy decisions was 8% to 14% across two studies.<sup>141,142,144</sup> Two further UK studies<sup>139,140,145</sup> reported changes from pre-test chemotherapy recommendation to the post-test decision, which may overestimate the net change: one reported a reduction of 23% in chemotherapy use<sup>139,140</sup> and the other assessed only patients with an initial recommendation for chemotherapy so it is misleading to calculate the absolute change.<sup>145</sup> Across 11 European (non-UK) studies,<sup>146–149,151–158</sup> the net reduction in chemotherapy recommendations or decisions ranged from 0% to 64%. Again, there was little clear difference in results in accordance with LN status.

### EndoPredict

In the one UK study of EndoPredict,<sup>159</sup> 37% of patients had a change in treatment decision (either to or from chemotherapy) (see *Table 27*). Across three European (non-UK) studies,<sup>160–162</sup> the percentage of patients with any change in treatment recommendation ranged from 38% to 41%. In the UK study, the net increase in chemotherapy use (pre test to post test) was 1% (because treatment changes took place in both directions).<sup>159</sup> However, across three European (non-UK) studies,<sup>160–162</sup> there was a net reduction in chemotherapy recommendations, ranging from 13% to 26%. There was insufficient data to assess results by lymph node status.

### IHC4+C

In the one UK study of IHC4+C (mix of LN+/LN0),<sup>163</sup> 27% of patients had a change in treatment recommendation (either to or from chemotherapy) (see *Table 28*). Pre-test decisions included either 'recommend chemotherapy' or 'discuss chemotherapy'. The net reduction in patients who were definitively recommended chemotherapy was 2%. However, if pre-test chemotherapy recommendations were assumed to include both 'recommend chemotherapy' and 'discuss chemotherapy', the net reduction could be up to 26%. There were no other European studies of IHC4.

TABLE 26 Decision impact results: oncotype DX

Study (first author and year)	Country	Population	Nodal status	Pre test	Post test	Number of patients	No chemotherapy, unchanged	No chemotherapy, changed to chemotherapy	Chemotherapy, unchanged	Chemotherapy, changed to no chemotherapy	Treatment change, n (%)	Pre-test chemotherapy, n (%)	Post-test chemotherapy, n (%)	Net change in chemotherapy, n (%)
<b>UK studies: recommendation</b>														
<sup>a</sup> Kiernan 2016 <sup>143</sup>	UK	ER+, HER2– (assumed)	LNO (assumed)	Recommendation	Recommendation	50	NR	NR	NR	NR	NR	21 (42) <sup>b</sup>	14 (28) <sup>b</sup>	–7 (–14)
Kuchel 2016 <sup>144</sup>	UK	ER+, HER2–	LNO–3	Recommendation	Recommendation	135	54	12	26	43	55 (41)	69 (51)	38 (28)	–31 (–23)
		ER+, HER2–, NPI intermediate	LNO–3	Recommendation	Recommendation	67	17	10	17	23	33 (49)	40 (60)	27 (40)	–13 (–19)
<b>UK studies: decision</b>														
Holt 2013, <sup>141</sup> Albanell 2016 <sup>142</sup>	UK	ER+, HER2– (subgroup)	LNO	Decision	Decision	94	45	9	18	22	31 (33)	40 (43)	27 (29)	–13 (–14)
Kuchel 2016 <sup>144</sup>	UK	ER+, HER2–	LNO–3	Decision	Decision	131	66	13	24	28	41 (31)	52 (40)	37 (28)	–15 (–11)
		ER+, HER2–, NPI intermediate	LNO–3	Decision	Decision	65	31	7	15	12	19 (29)	27 (42)	22 (34)	–5 (–8)
<b>UK studies: recommendation to decision</b>														
Hassan 2015, <sup>139</sup> Hassan 2015 <sup>140</sup>	UK	ER+, HER2– (assumed)	LNO (assumed)	Recommendation	Decision	26	9	2	7	8	10 (38)	15 (58)	9 (35)	–6 (–23)
Loncaster 2017 <sup>145</sup>	UK	ER+, HER2–	LNO	Recommendation	Decision (largely on test)	136	NR	NR	NR	NR	NR	136 (100)	54 (40)	N/A
			LN+			65	NR	NR	NR	NR	NR	65 (100)	20 (31)	N/A
<b>European studies: recommendation</b>														
Albanell 2012 <sup>146</sup> (trans-GEICAM)	Spain	ER+, HER2–	LNO	Recommendation	Recommendation	107	56	12	17	22	34 (32)	39 (36)	29 (27)	–10 (–9)
Dieci 2016 <sup>149</sup>	Italy	ER+, HER2–	LNO	Recommendation	Recommendation	123	71	5	37	10	15 (12)	47 (38)	42 (34)	–5 (–4)
Eiermann 2013 <sup>151</sup>	Germany	ER+, HER2–	LNO	Recommendation	Recommendation	244	99	28	72	45	73 (30)	117 (48)	100 (41)	–17 (–7)
Hejduk 2016, <sup>153</sup> Petrakova 2016 <sup>154</sup>	Czech Republic	ER+, HER2–	LNO	Recommendation	Recommendation	196	43	3	27	123	126 (64)	150 (77)	30 (15)	–120 (–61)

continued

**TABLE 26** Decision impact results: oncotype DX (continued)

Study (first author and year)	Country	Population	Nodal status	Pre test	Post test	Number of patients	No chemotherapy, unchanged	No chemotherapy, changed to chemotherapy	Chemotherapy, unchanged	Chemotherapy, changed to no chemotherapy	Treatment change, n (%)	Pre-test chemotherapy, n (%)	Post-test chemotherapy, n (%)	Net change in chemotherapy, n (%)
Gligorov 2015 <sup>152</sup> (SWITCH)	France	ER+, HER2-	LN0micro	Recommendation	Recommendation	95	41	5	19	30	35 (37)	49 (52)	24 (25)	-25 (-26)
Novas 2016 <sup>156</sup>	Spain	NR	LN1micro	Recommendation	Recommendation	35	21	1	5	8	9 (26)	13 (37)	6 (17)	-7 (-20)
Bodmer 2015 <sup>147</sup>	Switzerland	ER+, HER2-	LN0 or LN+	Recommendation	Recommendation	60	19	3	13	25	28 (47)	38 (63)	16 (27)	-22 (-37)
Dreyfus 2015 <sup>150</sup>	France	HR+, HER2- Indicated for chemotherapy	<ul style="list-style-type: none"> <li>LN0, 39%</li> <li>LN1-3, 51%</li> </ul>	Recommendation	Recommendation	39	0	0	13	26	26 (67)	39 (100)	13 (33)	N/A
Mouysset 2016 <sup>155</sup>	France	ER+, HER2-	<ul style="list-style-type: none"> <li>LN0, 61%</li> <li>LN+, 39%</li> </ul>	Recommendation	Recommendation	603	NR	NR	NR	NR	425 (70)	529 (88)	145 (24)	-384 (-64)
Pestalozzi 2015 <sup>157</sup>	Switzerland	ER+, HER2-	pN0 or pN1a	Recommendation	Recommendation	221	124	8	52	37	45 (20)	89 (40)	60 (27)	-29 (-13)
Wassermann 2015 <sup>158</sup>	France	HR+, HER2-	<ul style="list-style-type: none"> <li>LN0, 86%</li> <li>LNmicro or 1-3, 14</li> </ul>	Recommendation	Recommendation	72	NR	NR	NR	NR	NR	41 (57)	14 (19)	-27 (-38)
Eiermann 2013 <sup>151</sup>	Germany	ER+, HER2-	LN1-3	Recommendation	Recommendation	122	18	12	58	34	46 (38)	92 (75)	70 (57)	-22 (-18)
<b>European studies: recommendation to decision</b>														
Dieci 2016 <sup>149</sup>	Italy	ER+, HER2-	LN0	Recommendation	Decision		73	3	31	16	19 (15)	47 (38)	34 (28)	-13 (-11)
Eiermann 2013 <sup>151</sup>	Germany	ER+, HER2-	LN0	Recommendation	Decision	244	NR	NR	NR	NR	NR	117 (48)	83 (34)	-34 (-14)
De San Vicente 2015 <sup>148</sup>	Spain	HR+, HER2- Intermediate oncotype DX	<ul style="list-style-type: none"> <li>LN0, 73%</li> <li>LN+, 27%</li> </ul>	Recommendation	Decision	37	27	1	8	1	2 (5)	9 (24)	9 (24)	0 (0)
Eiermann 2013 <sup>151</sup>	Germany	ER+, HER2-	LN1-3	Recommendation	Decision	122	NR	NR	NR	NR	NR	92 (75)	57 (47)	-35 (-29)

ET, endocrine therapy; N/A, not applicable; NR, not reported.  
a Pre-/post-test chemotherapy includes 'chemotherapy recommended' and 'bias towards chemotherapy recommended', and pre-/post-test no chemotherapy includes 'ET alone advised' and 'bias towards ET alone'.

**TABLE 27** Decision impact results: EndoPredict (EPclin)

Study (first author and year)	Country	Population	Nodal status	Pre test	Post test	Number of patients	No chemotherapy, unchanged	No chemotherapy, changed to chemotherapy	Chemotherapy, unchanged	Chemotherapy, changed to no chemotherapy	Treatment change, n (%)	Pre-test chemotherapy, n (%)	Post-test chemotherapy, n (%)	Net change in chemotherapy, n (%)
<b>UK studies: decision</b>														
Bloomfield 2017 <sup>159</sup>	UK	ER+, HER2-	NR	Decision	Decision	149	60	28	34	27	55 (37)	61 (41)	62 (42)	+1 (+1)
<b>European studies: recommendation</b>														
Penault-Llorca 2016 <sup>162</sup> (ADENDOM)	France	ER+, HER2-	LN0micro	Recommendation	Recommendation	200	85	20	40	55	75 (38)	95 (48)	60 (30)	-35 (-18)
Ettl 2015 <sup>160</sup>	Germany	ER+, HER2-	<ul style="list-style-type: none"> <li>• LN0, 73%</li> <li>• LN+, 27%</li> </ul>	Recommendation	Recommendation	217	NR	16	NR	73	89 (41)	NR	NR	-57 (-26)
Muller 2013 <sup>161</sup>	Germany	ER+, HER2-	<ul style="list-style-type: none"> <li>• LN0, 62%</li> <li>• LN1-3, 35.5%</li> <li>• LN4+, 2.5%</li> </ul>	Recommendation	Recommendation	130	31	16	50	33	49 (38)	83 (64)	66 (51)	-17 (-13)
<b>European studies: recommendation to decision</b>														
Penault-Llorca 2016 <sup>162</sup> (ADENDOM)	France	ER+, HER2-	LN0micro	Recommendation	Decision	200	90	15	38	57	72 (36)	95 (48)	53 (27)	-42 (-21)
NR, not reported.														

TABLE 28 Decision impact results: IHC4+C

Study (first author and year)	Country	Population	Nodal status	Pre test	Post test	Number of patients, n	No chemotherapy, unchanged	No chemotherapy, changed to chemotherapy	Chemotherapy, unchanged	Chemotherapy, changed to no chemotherapy	Treatment change, n (%)	Pre-test chemotherapy, n (%)	Post-test chemotherapy, n (%)	Net change in chemotherapy, n (%)
<b>UK studies: recommendation</b>														
<sup>a</sup> Yeo 2015 <sup>163</sup>	UK	ER+ HER2-	LN0, 74%; LN1-3, 26%	Recommendation	Recommendation	124	49	1	41	33	34 (27)	45 (36) to 74 (60) <sup>a</sup>	42 (34)	-3 (-2) to -32 (-26)
<b>European studies</b>														
None														
NR, not reported.														
a Pre-test chemotherapy: lower estimate includes only those classed as 'recommend chemotherapy' and upper estimate includes both those classed as 'recommend chemotherapy' and 'discuss chemotherapy'.														

TABLE 29 Decision impact results: Prosigna

Study (first author and year)	Country	Population	Nodal status	Pre test	Post test	Number of patients	No chemotherapy, unchanged	No chemotherapy, changed to chemotherapy	Chemotherapy, unchanged	Chemotherapy, changed to no chemotherapy	Treatment change, n (%)	Pre-test chemotherapy, n (%)	Post-test chemotherapy, n (%)	Net change in chemotherapy, n (%)
<b>UK studies</b>														
None														
<b>European studies: recommendation</b>														
Martin 2015 <sup>164</sup> (GEICAM)	Spain	ER+, HER2-	LN0	Recommendation	Recommendation	200	122	18	38	22	40 (20)	60 (30)	56 (28)	-4 (-2)
Wuerstlein 2016 <sup>166</sup>	Germany	ER+, HER2-	LN0	Recommendation	Recommendation	198	131	22	40	5	27 (14)	45 (23)	62 (31)	+17 (+9)
Van Asten 2016 <sup>165</sup>	Belgium	ER+, HER2-	NR	Recommendation	Recommendation	51	15	11	15	10	21 (41)	25 (49)	26 (51)	+1 (+2)
NR, not reported.														

TABLE 30 Decision impact results: MammaPrint

Study (first author and year)	Country	Population	Nodal status	Pre test	Post test	Number of patients	No chemotherapy, unchanged	No chemotherapy, changed to chemotherapy	Chemotherapy, unchanged	Chemotherapy, changed to no chemotherapy	Treatment change, n (%)	Pre-test chemotherapy, n (%)	Post-test chemotherapy, n (%)	Net change in chemotherapy, n (%)
<b>UK studies</b>														
None														
<b>European studies: recommendation</b>														
<sup>a</sup> Drukker 2014 <sup>168</sup> (RASTER)	The Netherlands, Germany, France, Italy, Portugal	ER+/ ER-, HER2+/ HER2-	LN0	Recommendation	Recommendation	37 (414) <sup>a</sup>	202	9	144	59	68 (16)	203 (49)	153 (37)	-50 (-12)
Exner 2014 <sup>169</sup>	Austria	ER+, HER2-	LN0	Recommendation	Recommendation	75	40	4	21	10	14 (19)	31 (41)	25 (33)	-6 (-8)
Bueno-de-Mesquita 2007 <sup>81</sup> (RASTER)	The Netherlands	• 80% ER+ • 84% HER2-	LN0micro	Recommendation	Recommendation	427	NR	NR	NR	NR	NR	186 (44)	219 (51)	+33 (+8)
<sup>b</sup> Cusumano 2014 <sup>167</sup>	The Netherlands, Belgium, Italy, Spain	ER+, HER2-	• LN0 • LN1-3	Recommendation	Recommendation	151 (453) <sup>a</sup>	149	68	161	75	143 (32)	236 (52)	229 (51)	-7 (-2)
<sup>c</sup> Kuijjer 2016 <sup>171</sup>	The Netherlands	ER+ (HER2 NR)	NR	Recommendation	Recommendation	377 <sup>c</sup>	69	38	114	156	194 (51)	270 (72)	152 (40)	-118 (-31)
Wuerstlein 2016 <sup>173</sup> (WSG PRIME)	Germany	HR+, HER2-	• LN0 (72%) • LN1-3 (28%)	Recommendation	Recommendation (unclear)	430	201	65	107	57	122 (28)	164 (38)	172 (40)	+8 (+2)
<b>European studies: recommendation to decision</b>														
Bueno-de-Mesquita 2007 <sup>81</sup> (RASTER)	The Netherlands	• 80% ER+ • 84% HER2-	LN0micro	Recommendation	Decision	427	206	35	167	19	54 (13)	186 (44)	202 (47)	+16 (+4)
Rullan 2016 <sup>172</sup>	Spain	HR+, HER2-	94% LN0micro	Recommendation	Decision	129	NR	NR	NR	NR	NR	119 (92)	45 (35)	-74 (-57)
<b>European studies: decision to recommendation</b>														
Hartmann 2012 <sup>170</sup>	Germany	HR+, HER2-	• LN0 • LN1-3	Decision	Recommendation	60	47	6	2	5	11 (18)	7 (12)	8 (13)	+1 (+2)
NR, not reported.														
<sup>a</sup> Drukker 2014 <sup>168</sup> : each of the 37 patients were analysed by up to 12 physicians, giving 414 data points.														
<sup>b</sup> Cusumano 2014 <sup>167</sup> : each patient was analysed three times at three different hospitals (in three countries) so 151 patients but 453 data points.														
<sup>c</sup> Kuijjer 2016 <sup>171</sup> : data presented here exclude 283 patients with pre-test chemotherapy decision recorded as 'unsure'.														

## Prosigna

There were no UK studies of Prosigna. Across three European (non-UK) studies (either LNO or lymph node status not reported),<sup>164–166</sup> the percentage with any change in treatment recommendation ranged from 14% to 41% (see *Table 29*). The net change in chemotherapy recommendations (pre test to post test) was a reduction of 2% in one study<sup>164</sup> and an increase of 2% to 9% in two studies.<sup>165,166</sup>

## MammaPrint

There were no UK studies of MammaPrint. Across seven European (non-UK) studies,<sup>81,167–171,173</sup> the percentage with any change in treatment recommendation or decision ranged from 13% to 51% (see *Table 30*). The net change in chemotherapy recommendations (pre test to post test) ranged from a reduction of 31% to an increase of 8% across six studies.<sup>81,167–169,171,173</sup> Again there were insufficient data to assess results by lymph node status.

## Summary and discussion of decision impact studies

The percentage of patients with any change in treatment recommendation or decision (either to or from chemotherapy) among UK studies was 29% to 49% across four *oncoType* DX studies,<sup>62,139–142,144</sup> 37% in one EndoPredict study<sup>159</sup> and 27% in one IHC4+C study.<sup>163</sup> Ranges across European (non-UK) studies were 5% to 70% for *oncoType* DX,<sup>146–157</sup> 38% to 41% for EndoPredict,<sup>160–162</sup> 14% to 41% for Prosigna<sup>164–166</sup> and 13% to 51% for MammaPrint.<sup>81,167–171,173</sup>

The net changes in the percentage of patients with a chemotherapy recommendation or decision (pre test to post test) among UK studies were a reduction of 8% to 23% across four *oncoType* DX studies,<sup>141–144</sup> an increase of 1% in one EndoPredict study<sup>159</sup> and a reduction of between 2% and 26% in one IHC4+C study (unclear owing to category definitions).<sup>163</sup> Net changes across European (non-UK) studies were a reduction of 0% to 64% for *oncoType* DX,<sup>146–149,151–158</sup> a reduction of 13% to 26% for EndoPredict,<sup>160–162</sup> a reduction of 2% to an increase of 9% for Prosigna<sup>164–166</sup> and a reduction of 31% to an increase of 8% for MammaPrint.<sup>81,167–169,171,173</sup>

## Anxiety and health-related quality of life

Six studies (reported in seven publications)<sup>159,164,166,174–177</sup> reported outcomes relating to anxiety (including worry and distress) and HRQoL (*Table 31*). Studies reporting outcomes such as decision conflict and patient satisfaction did not meet the inclusion criteria for the review and were excluded.

### OncoType DX

Two studies<sup>174,176</sup> reported data for *oncoType* DX. Both adopted a pre–post test design, and included LN+ or LNO patients. Evans *et al.*<sup>174</sup> used the Impact of Events Scale<sup>178</sup> and showed no difference between pre- and post-test values ( $p = 0.09$ ), and there were no differences by recurrence score risk group (interaction tests reported as ‘not statistically significant’). Lo *et al.*,<sup>176</sup> on the other hand, reported a statistically significant improvement in overall State–Trait Anxiety Inventory (STAI) score between pre- and post-test values ( $p = 0.007$ ), but no difference in trait anxiety ( $p = 0.27$ ). Results for state anxiety were not reported. Only Lo *et al.*<sup>176</sup> reported HRQoL using Functional Assessment of Cancer Therapy – Breast cancer (FACT-B) and Functional Assessment of Cancer Therapy – General (FACT-G) and reported no statistically significant change ( $p = 0.55$  and  $p = 0.49$ , respectively) (*Table 32*).

### MammaPrint

One study reported data for MammaPrint<sup>177</sup> (see *Table 31*). The study recruited exclusively from patients who had been screened for eligibility in the MINDACT trial, but included both those eligible and those ineligible for MINDACT (due to having more than three positive lymph nodes or having a test failure). A modified version of Lynch’s distress scale<sup>179</sup> and one of Lerman’s Cancer Worry Scale<sup>180</sup> were used. Patients were separated into seven subgroups in accordance with their clinical risk, MammaPrint risk, whether or not they were assigned to chemotherapy and whether or not the MammaPrint test result

**TABLE 31** Study and patient characteristics: anxiety and HRQoL

Reference (first author and year)	Test	Cohort	Country	Study design	Details of test	Cut-off points	Number of patients	Population	Nodal status	Outcomes
<b>Oncotype DX</b>										
Evans 2016 <sup>174</sup>	Oncotype DX	Four centres (Washington, Maryland and Florida)	USA	Pre–post test	NR	NR	193	<ul style="list-style-type: none"> <li>ER+</li> <li>Stage I and II</li> </ul>	LN+/LN0 (LN > 3 NR)	IES <sup>178</sup>
Lo 2010 <sup>176</sup>	Oncotype DX	NR	USA	Pre–post test	Genomic Health	NR	93	<ul style="list-style-type: none"> <li>ESBC</li> <li>HER2+ 7%</li> </ul>	LN+/LN0 (LN > 3 NR)	STAI; FACT-B, FACT-G
<b>MammaPrint</b>										
Retèl 2013 <sup>177</sup>	MammaPrint	MINDACT-enrolled and MINDACT-ineligible patients	The Netherlands	Non-randomised clinical trial	NR	NR	347	ESBC	LN+/LN0	Lynch's distress scale (adapted); Lerman's Cancer Worry Scale (adapted); FACT-B breast cancer subscale
<b>EPclin</b>										
Bloomfield 2017 <sup>159,175</sup>	EPclin (EndoPredict plus NS plus TS)	Eight hospitals	South-east England	Pre–post test	NR	NR	149	<ul style="list-style-type: none"> <li>ER+</li> <li>HER2–</li> <li>ESBC with equivocal indications for chemotherapy by AOL</li> </ul>	NR	STAI
<b>Prosigna</b>										
Martin 2015 <sup>164</sup>	Prosigna	15 centres	Spain	Pre–post test	Manufacturer's specifications	NR	200	<ul style="list-style-type: none"> <li>ER+</li> <li>HER2–</li> <li>ESBC</li> <li>Stage I and II</li> </ul>	LN0	STAI; FACT-G
Wuerstlein 2016 <sup>166</sup>	Prosigna	11 centres	Germany	Pre–post test	Manufacturer's specifications	40–60	198	<ul style="list-style-type: none"> <li>ER+</li> <li>LN0</li> <li>Postmenopausal</li> </ul>	LN0	STAI; FACT-G
ESBC, early-stage breast cancer; FACT-B, Functional Assessment of Cancer Therapy – Breast cancer; FACT-G, Functional Assessment of Cancer Therapy – General; IES, Impact of Event Scale; NR, not reported; NS, nodal status; STAI, State–Trait Anxiety Inventory; TS, tumour size; WSG BCIST West German Study Group Breast Cancer Intrinsic Subtype Study.										

TABLE 32 Results: anxiety and HRQoL

Reference (first author and year)	Test	Country	Study design	Population	Nodal status	Anxiety	HRQoL
<b>Oncotype DX</b>							
Evans 2016 <sup>174</sup> <i>n</i> = 193	Oncotype DX	USA	PPT	ER+	LN+/LN0 (LN > 3 NR)	<ul style="list-style-type: none"> <li>• IES</li> <li>• No change pre–post test, <i>p</i> = 0.09. Not different by RS group (interaction tests not significant)</li> </ul>	NR
Lo 2010 <sup>176</sup> <i>n</i> = 93	Oncotype DX	USA	PPT	<ul style="list-style-type: none"> <li>• ESBC</li> <li>• HER2+ 7%</li> </ul>	LN+/LN0 (LN > 3 NR)	STAI mean score (SD) <ul style="list-style-type: none"> <li>• Pre: 39.6 (14.5)</li> <li>• Immediately post: 36 (12.6)</li> <li>• 12 months post: 34.0 (11.5), <i>p</i> = 0.007</li> </ul> Trait anxiety, mean (SD) <ul style="list-style-type: none"> <li>• Premenopausal: 32.2 (14.5)</li> <li>• Immediately post: 31.7 (13.3)</li> <li>• 12 months post: 33.2 (11.0), <i>p</i> = 0.27</li> </ul>	FACT-B mean score (SD) <ul style="list-style-type: none"> <li>• Pre: 112.2 (17.4)</li> <li>• 12 months post: 114.3 (18.6), <i>p</i> = 0.55</li> </ul> FACT-G mean score (SD) <ul style="list-style-type: none"> <li>• Pre: 88.7 (12.3)</li> <li>• 12 months post: 87.6 (14.9), <i>p</i> = 0.49</li> </ul>
<b>MammaPrint</b>							
Retèl 2013 <sup>177</sup> <i>n</i> = 347	MammaPrint	The Netherlands	Non-randomised clinical trial	ESBC	LN+/LN0	Lynch's distress scale (adapted) Adjusted regression analysis: <sup>a</sup> <ul style="list-style-type: none"> <li>• C high/G high: <i>p</i> &lt; 0.001</li> <li>• C low/G high (no chemotherapy): <i>p</i> = 0.043</li> <li>• C low/G high (chemotherapy): <i>p</i> &lt; 0.001</li> <li>• C high/G low (no chemotherapy): <i>p</i> &lt; 0.001</li> <li>• C high/G low (chemotherapy): <i>p</i> = 0.175</li> <li>• C low/G NA: <i>p</i> &lt; 0.001</li> <li>• C high/G NA: <i>p</i> &lt; 0.001</li> </ul> Lerman's Cancer Worry Scale (adapted) Adjusted regression analysis: <sup>a</sup> <ul style="list-style-type: none"> <li>• No risk group statistically significant (<i>p</i>-values ranged from 0.081 to 0.827)</li> </ul>	FACT-B, breast cancer subscale Adjusted regression analysis: <sup>a</sup> <ul style="list-style-type: none"> <li>• C high/G high: <i>p</i> = 0.013</li> <li>• C low/G high (no chemotherapy): <i>p</i> = 0.585</li> <li>• C low/G high (chemotherapy): <i>p</i> = 0.254</li> <li>• C high/G low (no chemotherapy): <i>p</i> = 0.541</li> <li>• C high/G low (chemotherapy): <i>p</i> = 0.296</li> <li>• C low/G NA: <i>p</i> = 0.075</li> <li>• C high/G NA: <i>p</i> &lt; 0.001</li> </ul>
<b>EPclin</b>							
Bloomfield 2017 <sup>159,175</sup> <i>n</i> = 149	EPclin	UK	PPT	ER+, HER2–, equivocal by AOL	NR	<ul style="list-style-type: none"> <li>• STAI</li> <li>• Unchanged decision: STAI stable</li> <li>• Change from chemotherapy to no chemotherapy: STAI lower (<i>p</i> &lt; 0.01)</li> <li>• Change from no chemotherapy to chemotherapy: STAI increase (<i>p</i> &lt; 0.001)</li> </ul>	NR

Reference (first author and year)	Test	Country	Study design	Population	Nodal status	Anxiety	HRQoL
<b>Prosigna</b>							
Martin 2015 <sup>164</sup>	Prosigna	Spain	PPT	ER+, HER2–	LNO	Trait anxiety, mean (SD) (n = 180)	FACT-G
n = 200						<ul style="list-style-type: none"> <li>Pre, all: 39.1 (11.1)</li> <li>Post: 39.2 (10.9)</li> <li>Difference: –0.1 (8.3), <i>p</i> = 0.858</li> </ul> State anxiety, mean (SD) (n = 181) <ul style="list-style-type: none"> <li>Pre: 42.6 (12.5)</li> <li>Post: 39.8 (13.3)</li> <li>Difference: 2.8 (12.4), <i>p</i> = 0.003; low <i>p</i> &lt; 0.001; intermediate <i>p</i> = 0.2; high <i>p</i> = 0.13</li> </ul>	<ul style="list-style-type: none"> <li>Pre: 79.2 (15.6)</li> <li>Post: 79.6 (14.6)</li> <li>Difference: –0.4 (13.9), <i>p</i> = 0.713</li> </ul>
Wuerstlein 2016 <sup>166</sup>	Prosigna	Germany	PPT	<ul style="list-style-type: none"> <li>ER+</li> <li>LNO</li> <li>Postmenopausal</li> </ul>	LNO	State anxiety, mean difference (SD)	FACT-G
n = 198						<ul style="list-style-type: none"> <li>Low ROR: –4.3 (8.9), <i>p</i> = 0.008</li> <li>Intermediate ROR: 0.3 (8), <i>p</i> = 0.639</li> <li>High ROR: 0.9 (11.6), <i>p</i> = 0.785</li> <li><i>p</i> = 0.001<sup>b</sup></li> </ul> Trait anxiety <ul style="list-style-type: none"> <li>No statistically significant difference in any group, <i>p</i> = 0.431<sup>b</sup></li> </ul>	No statistically significant differences in any group, for any subscale, except emotional and functional well-being <ul style="list-style-type: none"> <li>Physical well-being: <i>p</i> = 0.969<sup>b</sup></li> <li>Social/family well-being: <i>p</i> = 0.739<sup>b</sup></li> <li>Emotional well-being: <i>p</i> = 0.030<sup>b</sup></li> <li>Functional well-being: <i>p</i> = 0.005<sup>b</sup></li> </ul>

ESBC, early-stage breast cancer; NR, not reported; NS, nodal status; PPT, pre–post test design; RS, recurrence score; SD, standard deviation; TS, tumour size.

a Adjusted for sociodemographic (age, marital status, children and education), information/knowledge levels, risk perception variables (understanding, results in first visit, knowledge, risk perception and satisfaction) and risk groups (as listed in table).

b *p*-value analysis of variance of mean differences.

was missing (see *Table 32*). Regression analyses adjusted for sociodemographics, understanding of genomic results, timing of test results, perceived risk and satisfaction with the process showed statistically significantly (the analysis plan set the significance  $p$ -value to  $< 0.01$  to avoid type I errors) higher distress when the genomic test failed, when the patient was categorised as high risk by both clinical scoring and MammaPrint and in patients with discordant results when the treatment matched the MammaPrint score (i.e. clinical low/genomic high, prescribed chemotherapy; clinical high/genomic low, not prescribed chemotherapy). Only patients with high clinical risk and no genomic test result or high clinical risk and high genomic risk had a statistically significant decrease in FACT-B HRQoL.

### EndoPredict

One study<sup>159</sup> reported data for EndoPredict (see *Table 31*). The study was a pre–post test design and reported a statistically significant decrease in STAI for those whose treatment decision changed from chemotherapy to no chemotherapy on the basis of EndoPredict ( $p < 0.01$ ), and an increase in STAI for those whose treatment decision changed from no chemotherapy to chemotherapy ( $p < 0.001$ ) (see *Table 32*).

### Prosigna

Two studies<sup>164,166</sup> reported data for Prosigna (see *Table 31*). Both adopted a pre–post test design and included only LNO patients. In both studies, there was no difference in trait anxiety scores ( $p = 0.858$ <sup>164</sup> and  $p = 0.431$ <sup>166</sup>), and in both studies state anxiety changed significantly in low-risk (by Prosigna) patients ( $p < 0.001$ <sup>164</sup> and  $p = 0.008$ <sup>166</sup>) but not in the intermediate- or high-risk groups (see *Table 32*). Both studies reported FACT-G; Martin *et al.*<sup>164</sup> reported no change in overall scores, whereas Wuerstein *et al.*<sup>166</sup> reported a statistically significant analysis of variance  $p$ -value for emotional and physical well-being ( $p = 0.030$ ,  $p = 0.005$ , respectively).

### Discussion

There were no data relating to the impact of IHC4 on anxiety or HRQoL. Other available data are limited in terms of study designs (pre–post test) and patient spectrum. The lack of a comparator makes it difficult to tell whether or not similar changes would have occurred were patients to have received a definitive decision based on their clinical risk factors alone. Across tests, and when reported, state anxiety decreased post test and total FACT-G generally stayed the same. The results for one study suggest that patients had higher distress when the genomic test failed, when the patient was deemed to be at high risk by both clinical scoring and genomic test and in patients with discordant results when the treatment matched the genomic score, although it was unclear if this was due to distress associated with change (in treatment decision) or a lack of trust in the genomic score.

### Conclusions

Genomic testing may reduce state anxiety in some patients in some contexts, but, generally, there was little impact on HRQoL.

### Time-to-test results

Two articles reported time to test results: Losk *et al.*<sup>181</sup> and Müller *et al.*<sup>161</sup> Losk *et al.*<sup>181</sup> reported factors associated with delays in chemotherapy initiation (defined as  $\geq 42$  days from surgery to chemotherapy) in breast cancer patients at a US cancer centre in 2011–13. Of 263 HR+, HER2– women receiving adjuvant chemotherapy, 82 had an onco $type$  DX test ordered. Of those for whom an onco $type$  DX test was ordered, 31% had a delay of  $\geq 42$  days to chemotherapy initiation, compared with 20% of patients for whom onco $type$  DX was not ordered. Müller *et al.*<sup>161</sup> reports the time to test result for EndoPredict. In this study, the median handling time was 3 working days (range 0–11 days), and 59% of tests were conducted in  $\leq 3$  days.

## Chapter 3 Cost-effectiveness

This chapter presents the methods and results of a de novo model-based health economic evaluation of each of the tumour profiling tests compared with current practice. A systematic review of economic analyses of tumour profiling tests for early-stage breast cancer, undertaken to inform the model structure published since NICE DG10,<sup>20</sup> is presented in *Appendix 6*. A critique of economic analyses made available to the EAG by the manufacturers of *oncotype DX*<sup>62</sup> and *MammaPrint*<sup>94</sup> and by the chief investigator of the *EndoPredict* decision impact study<sup>182</sup> is presented in *Appendix 7*.

### Independent economic evaluation

#### Scope of the External Assessment Group economic analysis

The EAG developed a de novo model to assess the cost-effectiveness of *oncotype DX*, *Prosigna*, *IHC4+C*, *EPclin* and *MammaPrint* versus current practice only. The scope of the EAG model is summarised in *Table 33*. The model assesses the health outcomes and costs associated with each strategy over a lifetime horizon from the perspective of the UK NHS and PSS. All costs and health outcomes are discounted at a rate of 3.5% per annum.

**TABLE 33** Scope of the EAG economic analysis

Element of economic analysis	Description
Population	<p>Women with ER+, HER2– and early-stage breast cancer (LN0–3)</p> <p>For <i>oncotype DX</i>, <i>Prosigna</i>, <i>IHC4+C</i> and <i>EPclin</i>, analyses are presented for three discrete patient subgroups:</p> <ol style="list-style-type: none"> <li>1. LN0 NPI <math>\leq 3.4</math> (clinical low risk)</li> <li>2. LN0 NPI <math>&gt; 3.4</math> (clinical intermediate risk)</li> <li>3. LN1–3 (clinical high risk)</li> </ol> <p>For the evaluation of <i>MammaPrint</i>, the modelled population reflects the ITT population of the MINDACT trial.<sup>98</sup> Additional analyses are also presented for the mAOL clinical high-risk subgroup and the mAOL clinical low-risk subgroups separately</p>
Interventions	<ol style="list-style-type: none"> <li>1. <i>Oncotype DX</i><sup>a</sup> (cut-off points: low, <math>&lt; 18</math>; intermediate, 18–30; high, <math>\geq 31</math>)</li> <li>2. <i>Prosigna</i> (cut-off points for LN0: low, 0–40; intermediate, 41–60; high, 61–100) (cut-off points for LN+: low, 0–15; intermediate, 16–40; high, 41–100)</li> <li>3. <i>IHC4+C</i> (cut-off points: low, <math>&lt; 10\%</math>; intermediate, 10–20%; high, <math>&gt; 20\%</math>)</li> <li>4. <i>EPclin</i> (cut-off point: 3.3)</li> <li>5. <i>MammaPrint</i> (cut-off point as per MINDACT trial<sup>98</sup>)</li> </ol>
Comparator	<p>The comparator for all analyses is current practice (including a mix of risk prediction tools and diagnostic guidelines)</p> <p>For <i>MammaPrint</i>, current practice is based on mAOL, as per the design of the MINDACT trial<sup>98</sup></p> <p>Because of evidence limitations,<sup>b</sup> the competing tests were not compared incrementally against one another</p>
Primary health economic outcome	Incremental cost per QALY gained
Perspective	NHS and PSS
Time horizon	Lifetime
Discount rate	3.5% per annum
Price year	2015/16

a RSPC (*oncotype DX* including clinicopathological factors) is considered within the sensitivity analyses.

b *MammaPrint* data derived from a different source than the other tests; TransATAC analysis is based on non-restricted data set with different numbers of samples available for each test.

Unit costs are valued at 2015/16 prices. The principal sources of evidence used to inform the analyses of *oncoType* DX, Prosigna, IHC4+C and EPclin are the TransATAC study<sup>46</sup> and the NHS England Access Scheme Database.<sup>183</sup> As the TransATAC study does not include the MammaPrint test, the MINDACT study<sup>98</sup> was instead used as the basis for estimating classification probabilities and conditional DMFS probabilities for MammaPrint. Additional studies identified within the clinical evidence review (see *Chapter 2*), which provide alternative relevant data on test risk classification probabilities, 10-year DMFS probabilities conditional on risk classification and post-test chemotherapy probabilities (decision impact) are explored within the sensitivity analyses.

### Population

The population reflected in the model relates to women with ER+, HER2– early-stage breast cancer with LN0–3. For *oncoType* DX, IHC4+C, Prosigna and EPclin, the economic analysis is presented for three discrete subgroups: (1) women with node-negative disease and a NPI of  $\leq 3.4$  (clinical low risk), (2) women with node-negative disease and a NPI of  $> 3.4$  (clinical intermediate risk) and (3) node positive (one to three nodes). The modelled population for these four tests reflects that of the TransATAC study,<sup>46</sup> as this is used as the source of data on risk classification for each test and the 10-year DMFS probability conditional on each risk classification. Within the LN0 population, a NPI cut-off point of 3.4 was chosen as a means of distinguishing between clinical low risk and clinical intermediate risk for *oncoType* DX, IHC4+C, Prosigna and EPclin, as data by NPI score were available from the TransATAC trial<sup>46</sup> and the National Cancer Registration and Analysis Service (NCRAS) cancer registration data set.<sup>184</sup> Predict scores were not available in either data set, so this tool could not be used to define clinical risk.

MammaPrint was not included in the TransATAC study, hence an alternative source was required. The economic analysis of MammaPrint was instead largely based on data reported within the original paper and supplementary material of the MINDACT trial publication.<sup>98</sup> As the randomisation schedule within the MINDACT trial was conducted using a modified version of AOL (mAOL) and sufficient data were not presented separately for patients with 1–3 lymph nodes, the population of the primary analysis largely reflects the MINDACT ITT population.<sup>98</sup> Additional analyses are also presented for the mAOL high-risk subgroup and the mAOL low-risk subgroups.

### Interventions

The EAG's economic analysis includes all five tests included in the final NICE scope<sup>21</sup> (see *Table 2*). The tests are modelled in line with how their manufacturers state that they will be used in clinical practice: IHC4 and EndoPredict are assumed to be applied together with clinicopathological factors (IHC4+C and EPclin, respectively). RSPC (*oncoType* DX in conjunction with clinicopathological factors) is considered separately within the sensitivity analyses but is not included in the EAG's base case. The EAG's economic analysis also assumes that all pathology analysis is undertaken centrally; local pathology analysis is not considered within the EAG's base case.

### Comparator

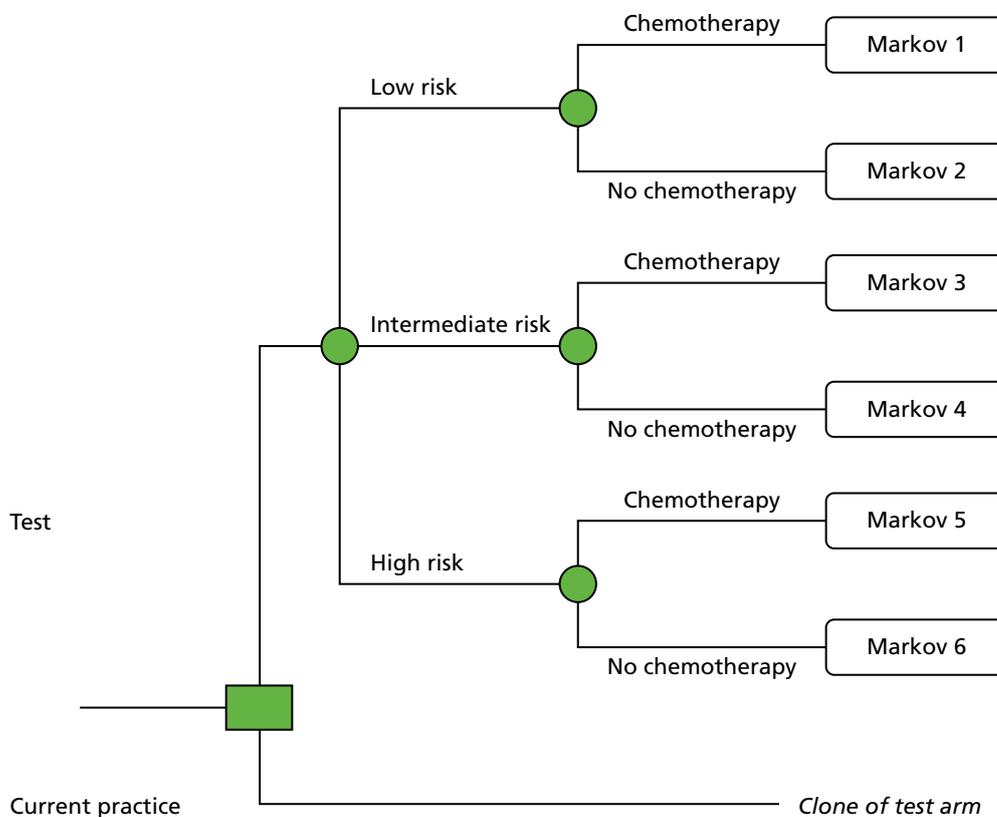
The most commonly used tools for predicting the ROR after surgery to guide the use of adjuvant chemotherapy for breast cancer in England are Predict and NPI. At the time of writing, AOL is being updated and has been temporarily disabled. As noted previously, a modified version of AOL was used to inform the randomisation schedule for the discordant clinical and genomic risk groups within the MINDACT trial.<sup>98</sup> For this reason, the comparator for the analysis of MammaPrint is current practice using mAOL.

Owing to the use of a different evidence source for MammaPrint<sup>98</sup> compared with the other four tumour profiling tests, and the use of the unrestricted TransATAC trial data set,<sup>46</sup> each test is compared only against current practice; tests were not assessed incrementally against each other.

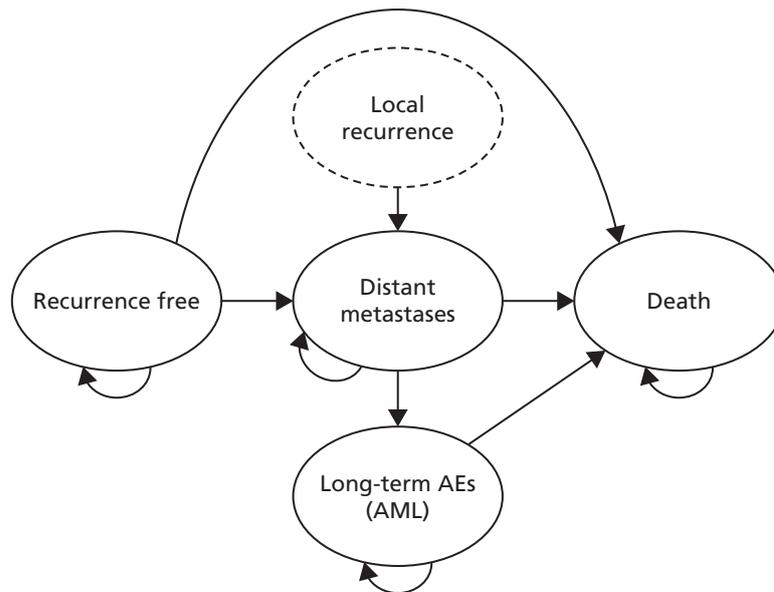
### Model structure

The general structure of the EAG model is based on the model previously developed by Ward *et al.*<sup>1</sup> to inform NICE DG10.<sup>20</sup> This is also broadly consistent with the majority of studies identified within the review of published economic evaluations (see *Appendix 6*). The EAG model takes the form of a hybrid decision-tree/Markov model (*Figures 5 and 6*). The decision tree component of the model classifies patients in the current practice (no test) group and the tumour profiling test group into high-, intermediate- and low-risk categories based on the results of the test. For EPclin and MammaPrint, the intermediate-risk category is not relevant as these tests provide results in terms of high and low risk only. The treatment group (test or no test) and the risk level predicted by the test determines the probability that the patient will subsequently receive adjuvant chemotherapy. Within both the test group and the current practice group, the decision tree determines the probability that a patient will be assigned to one of six groups: (1) low risk, chemotherapy; (2) low risk, no chemotherapy; (3) intermediate risk, chemotherapy; (4) intermediate risk, no chemotherapy; (5) high risk, chemotherapy; and (6) high risk, no chemotherapy (for the analyses of EPclin and MammaPrint, four branches are used owing to the absence of an intermediate-risk category). Each of the branches is then linked to a Markov model that predicts lifetime QALYs and costs in accordance with the patient's risk of distant recurrence and whether or not they receive chemotherapy.

*Figure 6* illustrates the Markov nodes of the model. Each Markov node is evaluated over 84 6-month cycles (42 years): patients are assumed to enter the model aged 58 years and the evaluation is continued until the cohort has reached the age of 100 years. Each Markov node includes four health states: (1) recurrence-free, (2) distant recurrence, (3) long-term AEs [acute myeloid leukaemia (AML)] and (4) death. Each Markov node differs with respect to the patient's risk of distant metastases (determined by their risk classification and whether or not they receive adjuvant chemotherapy). For all Markov nodes, patients enter the model in the recurrence-free health state. During any 6-month cycle, patients who are recurrence-free can remain in their current health state, transit to the long-term AEs state, develop distant metastases or die. Patients in the distant metastases state can remain in their current health state, transit to the long-term AEs (AML)



**FIGURE 5** The EAG model: decision tree component. For EPclin and MammaPrint, four branches are used owing to the absence of an intermediate-risk category for these tests.



**FIGURE 6** The EAG model: state-transition model component. AML, acute myeloid leukaemia.

state or die. Patients in the long-term AEs (AML) state are assumed to remain in this state until death (if free from breast cancer recurrence, they cannot subsequently develop distant metastases owing to their breast cancer). Patients may die because of breast cancer, AML or other causes. A HRQoL decrement is applied during the first model cycle for patients receiving adjuvant chemotherapy to account for health losses associated with short-term chemotherapy-related AEs. The benefit of adjuvant chemotherapy is modelled using a RR of distant recurrence within each risk classification group. The impact of each test is therefore captured in the model only by changing the probability that patients with each test risk classification receive adjuvant chemotherapy. In the evaluation of *oncotype DX*, a sensitivity analysis is included in which the test is assumed to provide a predictive benefit of chemotherapy, hence different RRs of developing distant metastases (for chemotherapy vs. no chemotherapy) are applied across the low-, intermediate- and high-risk groups.

Different health utilities are applied to each of the modelled health states. The model assumes that a proportion of patients who experience distant recurrence will also have previously developed local recurrence: this is assumed to be associated with additional costs and a once-only QALY loss. The model includes costs associated with the tumour profiling test (in the intervention group only), adjuvant chemotherapy acquisition and administration and associated toxicity, endocrine therapy (all patients), routine follow-up visits and tests, additional therapies [zoledronic acid and granulocyte colony-stimulating factor (G-CSF)], treatments for local recurrence and treatments for distant metastases. The costs and health outcomes for each Markov node differ owing to the different risks of recurrence associated with each tumour profiling test and whether or not chemotherapy is given (together with its associated benefits, AEs and costs).

### Key External Assessment Group model assumptions

The EAG model makes the following structural assumptions:

- Within the base-case analysis, the proportion of patients who receive chemotherapy under current practice (no test) is assumed to be the same for each test risk classification (low, intermediate and high risk). However, this proportion is assumed to differ between subgroups defined in accordance with clinical risk (LN0 NPI  $\leq 3.4$ , LN0 NPI  $> 3.4$ , LN1–3, MINDACT ITT, MINDACT mAOL low risk and MINDACT mAOL high risk).

- The model assumes that clinicians interpret each of the three-level tests in the same way (e.g. an *oncotype* DX high-risk score would lead to the same chemotherapy decision as a *Prosigna* high-risk score). The model also assumes that clinicians interpret each of the two-level tests in the same way (a *MammaPrint* high-risk score would lead to the same chemotherapy decision as an *EPclin* high-risk score).
- Within the base-case analysis, the relative benefit of adjuvant chemotherapy is assumed to be the same across all risk score categories for all tests (the same RR is applied to all patients, irrespective of test risk score). The impact of assuming a predictive benefit for *oncotype* DX, which is applied by assuming different RRs between test risk score categories, is explored within the sensitivity analyses.
- The impact of the tests is modelled by changing which patients receive adjuvant chemotherapy.
- A proportion of patients who develop distant metastases are assumed to have previously developed local recurrence. Local recurrence is not modelled as a separate event or health state. QALY losses and costs associated with local recurrence are applied once only (on entry into the distant metastases state).
- A disutility associated with short-term AEs related to adjuvant chemotherapy is applied once during the first model cycle only (while the patient is receiving treatment).
- Patients can enter the long-term AEs (AML) health state from either the recurrence-free state or the distant metastases state. The prognosis of patients with AML and the costs and QALYs accrued within the AML state are assumed to be independent of whether or not the patient has previously developed distant metastases due to their breast cancer. Once a patient develops AML, the model assumes that this alone determines their survival prognosis. Although congestive heart failure (CHF) is also a potentially relevant long-term AE associated with chemotherapy, this was excluded from the model owing to a lack of evidence on the joint survival impact of CHF and metastatic breast cancer. The importance of AEs not included in the model on the cost-effectiveness of the tests is explored within sensitivity analyses.
- Costs associated with endocrine therapy, bisphosphonates (zoledronic acid), follow-up appointments and mammograms are assumed to differ in accordance with time since model entry.
- Across all three analysis subgroups, patients are assumed to enter the model aged 58 years, based on the mean age of patients in the NHS England Access Scheme Database<sup>183</sup> (rounded down to an integer value).
- The model includes both premenopausal and postmenopausal women. However, the *TransATAC* study relates only to postmenopausal women.

### Evidence sources used to inform the model parameters

*Table 34* summarises the evidence sources used to inform the parameters of the EAG model. The individual parameter values are discussed in further detail in the subsequent sections; data tables relating to these model inputs can be found in *Appendix 8*.

### Patient age

The mean age was assumed to be 58 years, based on the NHS England Access Scheme Database<sup>183</sup> (rounded down to an integer value).

### Risk classification probabilities using each test: *oncotype* DX, *Prosigna*, *IHC4+C* and *EPclin*

Data relating to risk classification probabilities for each test were obtained from a bespoke analysis of the *TransATAC* trial provided by the trial investigators<sup>46</sup> (see *Appendix 8, Table 76*). As discussed in *Chapter 2*, the *ATAC* trial evaluated the efficacy and safety of anastrozole versus tamoxifen. The *TransATAC* trial tested tumour blocks from postmenopausal patients who had been included in the monotherapy arms of the *Arimidex, Tamoxifen, Alone or in Combination (ATAC)* trial<sup>198</sup> in order to determine whether or not the tests could provide independent information on the risk of distant recurrence. Separate data analyses were provided by the trial investigators for ER+, HER2– patients for the three modelled subgroups [LN0 NPI ≤ 3.4, LN0 NPI > 3.4 and LN1–3]. In order to maximise the information available for each test, data were not restricted to only those with information on all four tests. The EAG considers that the use of this study has particular value as (1) it includes the use of four of the five tests included in the final NICE scope (*oncotype* DX, *Prosigna*, *IHC4+C* and *EPclin*) within the same patient population, (2) it provides a source of data on

TABLE 34 Evidence sources used in the model

Parameter group	Source
Patient age	Based on the NHS England Access Scheme Database <sup>183</sup>
Risk classification probabilities for <i>oncotype</i> DX, EPclin, Prosigna and IHC4+C	TransATAC bespoke data request. <sup>46</sup> Analysed by subgroup [LN0 NPI $\leq$ 3.4, LN0 NPI > 3.4 and LN1–3]
Risk classification probabilities for MammaPrint	MINDACT. <sup>98</sup> Analysed in accordance with ITT trial population and mAOL low-risk and high-risk subgroups
Distant recurrence rates (10 years) conditional on test risk classification ( <i>oncotype</i> DX, EPclin, Prosigna and IHC4+C)	TransATAC bespoke data request. <sup>46</sup> Analysed by subgroup [LN0 NPI $\leq$ 3.4, LN0 NPI > 3.4 and LN1–3]
Distant recurrence rates (10 years) conditional on test risk classification (MammaPrint)	MINDACT. <sup>98</sup> Analysed in accordance with ITT trial population and mAOL low-risk and high-risk subgroups. All analyses involve extrapolation from the 5-year data
Baseline probability of receiving adjuvant chemotherapy (current practice)	LN0 NPI $\leq$ 3.4 subgroup: NCRAS bespoke data request <sup>184</sup>
	LN0 NPI > 3.4 subgroup: NHS England Access Scheme Database <sup>183</sup>
	LN1–3 subgroup: NCRAS bespoke data request <sup>184</sup>
	MINDACT population (MammaPrint only): clinical judgement (Professor Robert Stein, UCL, 2017, estimates weighted by proportion with LN0 and LN+ disease and mAOL low risk/high risk)
Probability of receiving chemotherapy conditional on results of test (three-level tests – <i>oncotype</i> DX, IHC4+C and Prosigna)	LN0 NPI $\leq$ 3.4 subgroup: UKBCG survey (see <i>Appendix 9</i> )
	LN0 NPI > 3.4 subgroup: NHS England Access Scheme Database <sup>183</sup>
	LN1–3 subgroup: Lancaster <i>et al.</i> <sup>145</sup>
Probability of receiving chemotherapy conditional on results of test (two-level tests – EPclin and MammaPrint)	Bloomfield <i>et al.</i> <sup>159</sup> Applied to all analysis subgroups
10-year relative ROR for chemotherapy vs. no chemotherapy	EBCTCG 2012 meta-analysis <sup>185</sup>
Predictive chemotherapy benefit: <i>oncotype</i> DX (applied in sensitivity analysis only)	LN0 subgroups: Paik <i>et al.</i> <sup>50</sup>
	LN1–3 subgroup: Albain <i>et al.</i> <sup>53</sup>
Probability of death following distant recurrence	Thomas <i>et al.</i> <sup>186</sup>
Probability of local recurrence	de Bock <i>et al.</i> <sup>187</sup>
Probability of AML	Wolff <i>et al.</i> <sup>188</sup>
Probability of death following onset of AML	Edlin <i>et al.</i> <sup>189</sup>
Other-cause mortality (life tables)	ONS <sup>190</sup>
HRQoL	Utility – recurrence-free and distant recurrence: Lidgren <i>et al.</i> <sup>191</sup>
	Utility AML: Younis <i>et al.</i> <sup>192</sup>
	HRQoL decrement – local recurrence and AEs related to adjuvant chemotherapy: Campbell <i>et al.</i> <sup>193</sup>
Tumour profiling test costs	Test manufacturers

**TABLE 34** Evidence sources used in the model (*continued*)

Parameter group	Source
Costs	
Adjuvant chemotherapy	Hall <i>et al.</i> <sup>30</sup>
Endocrine therapy	BNF <sup>194</sup>
G-CSF	BNF <sup>194</sup> and PSSRU <sup>195</sup>
Routine follow-up	<i>NHS Reference Costs 2015/16</i> <sup>196</sup> and Campbell <i>et al.</i> <sup>193</sup>
Bisphosphonates (zoledronic acid)	BNF <sup>194</sup> and <i>NHS Reference Costs 2015/16</i> <sup>196</sup>
Local recurrence	Karnon <i>et al.</i> <sup>197</sup>
Distant metastases	Thomas <i>et al.</i> <sup>186</sup>

BNF, *British National Formulary*; ONS, Office for National Statistics; PSSRU, Personal Social Services Research Unit; UCL, University College London; UKBCG, UK Breast Cancer Group.

10-year DMFI probabilities conditional on test risk classification, thereby avoiding confounding due to the use of different evidence sources for these parameters, and (3) TransATAC is a large UK study. However, two caveats should be noted with respect to the choice of this data source. First, the non-restricted TransATAC data set was used for the analysis – this maximises the sample size for each individual test; however, as each additional test was analysed, more tissue was required and for some samples insufficient tissue was left. This reduces the number of patients with available data and may introduce bias comparing across tests. In addition, whereas the ATAC trial included only postmenopausal women, the economic analysis assumes that the risk classification and DMFI probabilities obtained from the TransATAC analysis can be translated to a premenopausal population; this assumption introduces an additional degree of uncertainty with respect to the generalisability of the analysis.

### Risk classification probabilities: MammaPrint

The evaluation of MammaPrint was based on the MINDACT trial.<sup>98</sup> This study was selected for inclusion in the analysis for three reasons: (1) the trial publication and supplementary material provide sufficient information to estimate risk classification probabilities and DMFS probabilities conditional on risk classification within the same patient populations, (2) it includes a large sample size and (3) the study allows for the estimation of the benefit of chemotherapy between discordant groups.

Risk classification probabilities for MammaPrint were obtained from the trial publication of the MINDACT trial<sup>98</sup> and the accompanying supplementary material (see *Appendix 8, Table 77*).

### Probability of developing distant metastases (without chemotherapy): oncotype DX, Prosigna, IHC4+C and EPclin

The probability of developing distant metastases was based on 10-year DMFI/DMFS outcomes for each test risk classification. For oncotype DX, Prosigna, IHC4+C and EPclin, these were obtained from a bespoke data analysis of the TransATAC study<sup>46</sup> (see *Appendix 8, Table 78*).

The 10-year DMFI probability was converted to a cumulative probability of recurrence for each test within each risk classification category (1 – DMFI) and converted to a 6-month probability of distant recurrence assuming a constant rate.

### Probability of developing distant metastases (without chemotherapy): MammaPrint

Cardoso *et al.*<sup>98</sup> report 5-year DMFS probabilities for patients who did, or did not, receive adjuvant chemotherapy in the discordant risk groups in the MINDACT trial.<sup>98</sup> Additional information is also provided on chemotherapy use and 5-year DMFS in the concordant risk groups. For the economic analysis based on

the MINDACT ITT population, it was necessary to estimate DMFS probabilities for all concordant and discordant groups in accordance with clinical and genomic risk classification and whether or not patients received chemotherapy. This was done as follows (refer to data presented in *Appendix 8, Table 79*):

- The 10-year DMFS outcomes were estimated for all concordant and discordant clinical and genomic risk groups in accordance with whether or not patients received adjuvant chemotherapy (EAG group labels A–H) based on 5-year DMFS outcomes, assuming a constant event rate. The proportions of patients who received chemotherapy were obtained from the supplementary material of the Cardoso *et al.*<sup>98</sup> trial publication. An adjustment was made to the mAOL high-risk, MammaPrint high-risk group to estimate counterfactual 10-year DMFS for patients not receiving chemotherapy (EAG group label H); this was done by estimating the 10-year DMFS probability for this group (with chemotherapy) and multiplying this value by the reciprocal of the estimated 10-year RR of distant metastases for chemotherapy versus no chemotherapy for the overall discordant population (RR 0.77, adjusted 10-year DMFS for group 0.766).
- The 10-year DMFS outcomes for the MammaPrint low-risk group (without adjuvant chemotherapy) were estimated by weighting the estimated 10-year DMFS probabilities for the MammaPrint low-risk no-chemotherapy groups (EAG group labels B and D) in accordance with the number of mAOL low-risk and high-risk patients in these groups.
- The 10-year DMFS outcomes for the MammaPrint high-risk group (without adjuvant chemotherapy) were estimated by weighting the estimated 10-year DMFS probabilities for the genomic high-risk no-chemotherapy groups (EAG group labels F and H, including the adjustment described above) in accordance with the number of mAOL low-risk and high-risk patients in these groups.

### Tapering of risk of recurrence over time

The EAG notes that there is uncertainty with respect to the long-term risk of distant recurrence. The EAG model makes the same assumptions regarding long-term distant metastasis risk as the previous model reported by Ward *et al.*<sup>1</sup> The model assumes that the risk of distant metastases between 10 and 15 years is equal to half of the risk during the preceding period (0–10 years); beyond 15-years, the risk of distant recurrence is assumed to be zero. The EAG notes that this is a simplification. This general decrease in the hazard of recurrence can be seen in the 10- to 15-year control arm annualised recurrence data reported in the 2005 EBCTCG meta-analysis.<sup>199</sup> Although there is some evidence that suggests that for some patients with particular disease subtypes, recurrence rates remain approximately constant between 5 and 20 years,<sup>200</sup> there is also uncertainty surrounding the duration over which the benefit of chemotherapy is sustained; hence, constraining recurrence at 15 years reduces the likelihood of overestimating this benefit of chemotherapy. The impact of removing this assumption of recurrence risk tapering is explored within the sensitivity analyses.

### Probability of receiving chemotherapy in the current practice group

The EAG identified two empirical sources that could be used to inform the probability that a patient receives chemotherapy without tumour profile testing: (1) the NCRAS data set<sup>184</sup> and (2) the NHS England Access Scheme Database (intermediate clinical risk only).<sup>183</sup> These alternative sources are discussed briefly in the following sections.

### National Cancer Registration and Analysis Service data set

A bespoke data request was placed with the NCRAS to obtain aggregate data relating to the use of adjuvant chemotherapy in women with early-stage breast cancer in England (see *Appendix 8, Table 80*). The NCRAS cancer registration data sets were used to estimate current levels of chemotherapy use in each of the three model subgroups [LN0 NPI  $\leq$  3.4, LN0 NPI  $>$  3.4 and LN1–3]. An age restriction of 55–75 years was applied with the intention of only selecting those patients who were sufficiently fit to undergo chemotherapy and therefore may benefit from tumour profile testing, and also of removing younger patients who are more likely to receive chemotherapy and are less reflective of the populations used to estimate risk classification probabilities and distant recurrence risk.<sup>46</sup> An additional data analysis on chemotherapy use for the whole population aged  $<$  75 years was also obtained. As shown in *Appendix 8, Table 80*, within the 55- to 75-year age group, the proportions of women receiving chemotherapy are 7.19%, 40.01% and 62.72% in the LN0

$NPI \leq 3.4$ , LN0  $NPI > 3.4$  and LN1–3 subgroups, respectively. As expected, the proportion of women receiving chemotherapy is higher in the broader aged  $\leq 75$  years population.

It should be noted that the NCRAS data set reflects an unselected population who are not necessarily eligible for tumour profile testing; this may increase the size of the denominator and, hence, in reality, the proportion of women who are eligible for testing who go on to receive adjuvant chemotherapy may be greater than the estimates generated using this data set.

### NHS England onco $type$ DX Access Scheme Database

The NHS England Access Scheme Database<sup>183</sup> contains data on the pre-test chemotherapy decision for women who received the onco $type$  DX test in England. It should be noted that this data set relates only to women who were deemed to be at intermediate clinical risk, hence the data may not provide a good reflection of pre- and post-test chemotherapy decision-making for women with LN0 disease and a NPI score of  $\leq 3.4$  or for women with LN+ disease. The pre-test probability of receiving adjuvant chemotherapy is 0.431. This estimate is only slightly higher than the estimate generated using the NCRAS data set<sup>184</sup> (probability of 0.40).

Within the EAG base-case analysis, the following selections were made:

- For the LN0  $NPI \leq 3.4$  subgroup, the NCRAS data set<sup>184</sup> was used as these are the only data on baseline chemotherapy use available for this patient subgroup.
- For the LN1–3 subgroup, the NCRAS data set<sup>184</sup> was used as these are the only data on baseline chemotherapy use available for this patient subgroup.
- For the LN0  $NPI > 3.4$  subgroup, the NHS England Access Scheme Database<sup>183</sup> was used. This source was selected on the basis of consistency: the same data set is used to inform the post-test probabilities of receiving chemotherapy conditional on risk score. It should also be noted that the collection of these data were requested by the NICE Diagnostics Appraisal Committee in NICE DG10.<sup>20</sup>
- For the MammaPrint analyses, the EAG is not aware of any empirical evidence source that provides estimates of baseline chemotherapy use (without testing) for patients who are mAOL high risk or mAOL low risk. For this reason, these parameters were informed by expert opinion (Professor Rob Stein, University College London, 2017, personal communication). The following estimates were applied in the model, based on the modified version of AOL applied in the MINDACT trial –
  - LN0, mAOL high risk, baseline chemotherapy probability = 70%
  - LN+, mAOL high risk, baseline chemotherapy probability = 90%
  - LN0, mAOL low risk, baseline chemotherapy probability = 15%
  - LN+, mAOL low risk, baseline chemotherapy probability = 30%.

These estimates were then weighted in accordance with the proportion of women with LN0 and LN+ disease within the overall MINDACT population and within the mAOL high-risk and low-risk subgroups. This leads to baseline probabilities of 0.46, 0.77 and 0.16 for the MINDACT overall trial population, the mAOL high-risk subgroup and the mAOL low-risk subgroup, respectively.

When appropriate, the source not selected for inclusion in the EAG base case was tested in the sensitivity analyses.

### Probability of receiving chemotherapy conditional on test risk classification

Based on the review of decision impact studies presented in *Chapter 2, Results: decision impact studies*, five UK-based sources relating largely to the three analysis subgroups [LN0  $NPI \leq 3.4$ , LN0  $NPI > 3.4$  and LN1–3] were identified as providing potentially usable data relating to the probability that a patient receives adjuvant chemotherapy conditional on the risk score given by the tumour profiling test. Evidence selection for these parameters was focused on UK-based studies as these are more likely to reflect how clinicians will use the tests in England, although European studies were considered when the UK-based

evidence was particularly limited (specifically for the two-level tests). The five UK-based studies identified are (1) the NHS England Access Scheme Database,<sup>183</sup> (2) Holt *et al.*,<sup>201</sup> (3) Lancaster *et al.*,<sup>145</sup> (4) Bloomfield *et al.*<sup>159</sup> and (5) the UK Breast Cancer Group (UKBCG) survey (see *Appendix 9*). The advantages and disadvantages of using each of these studies are summarised in *Table 35*.

**TABLE 35** Studies available to inform chemotherapy use conditional on test results

Study	Disease type	EAG comments
NHS England Access Scheme Database <sup>183</sup>	LNO, intermediate clinical risk	<p>This data collection exercise was requested by the NICE Diagnostics Appraisal Committee within the guidance for NICE DG10.<sup>20</sup> The data set includes only patients with intermediate clinical risk and is likely to be relevant only to patients with LNO disease and a NPI of &gt; 3.4. The data relate to the actual chemotherapy decision rather than a recommendation</p> <p>The NHS England Access Scheme data were provided as AiC and cannot be reported here</p>
Holt <i>et al.</i> <sup>201</sup>	LNO or pN1mic (micrometastasis)	<p>Prospective UK clinical study of the impact of onco<sup>type</sup> DX on adjuvant treatment decisions and risk classification by NPI and onco<sup>type</sup> DX recurrence score. Results were available for 74 patients. The data relate to the chemotherapy recommendation rather than the final decision. The EAG notes that this study has been published only in abstract form and few details are available regarding the methods</p>
Bloomfield <i>et al.</i> <sup>159</sup>	Unclear	<p>UK study of decision impact of EndoPredict. Fourteen oncologists in eight UK hospitals saw 149 patients judged by clinical teams to have equivocal indications for chemotherapy. Patients and oncologists discussed provisional treatment decisions based on conventional prognostic factors. Initial decisions were reconsidered when EndoPredict results were available. The data appear to relate to the final decision rather than recommendations</p> <p>The EAG notes that this is the only available UK study that relates to decision impact with a two-level tumour profiling test. The population relates to patients for whom there was no clear decision on whether or not chemotherapy should be given. This study is unlikely to accurately represent the use of chemotherapy in women with LN+ disease</p>
Lancaster <i>et al.</i> <sup>145</sup>	LNO and LN+	<p>A prospective UK pilot study designed to evaluate the clinical value of onco<sup>type</sup> DX testing. Testing was carried out in 201 women with newly diagnosed, ER+, HER2-, invasive breast cancer who underwent breast surgery with curative intent. Separate estimates are provided for the LNO and LN+ subgroups. The data appear to relate to recommendations rather than the final decision</p> <p>The EAG notes that patients enrolled in this study had already been recommended chemotherapy, therefore the use of this study may exaggerate the proportion of women for whom the final decision was to receive chemotherapy</p>
UKBCG survey (see <i>Appendix 9</i> )	LNO NPI ≤ 3.4, LNO NPI > 3.4 and LN1–3	<p>The UKBCG network disseminated a bespoke unfunded survey designed by the EAG to its members (see <i>Appendix 9</i>). Respondents were asked 'Based on your own subjective opinion, please estimate the probability that a woman in each of these subgroups and with each genomic/immunohistochemical test result would go on to receive adjuvant chemotherapy'. Responses were requested for two-level and three-level tests for the LNO NPI ≤ 3.4, LNO NPI &gt; 3.4 and LN1–3 subgroups. Eleven usable responses were received from participating oncologists</p> <p>The results indicate considerable variation in practice. Several respondents noted uncertainty with respect to the two-level tests as they do not currently have access to these technologies</p>

Estimates of the use of adjuvant chemotherapy conditional on test risk classification based on these alternative sources are summarised in *Appendix 8, Table 81*.

With respect to the EAG base case, the following study selections were made:

- For the use of the three-level tests (onco*type* DX, Prosigna and IHC4+C) in the LN0 NPI  $\leq 3.4$  subgroup, the UKBCG survey data were used. This selection was made owing to the absence of any published UK evidence on the decision impact of tumour profiling tests in this patient subgroup.
- For the use of the three-level tests (onco*type* DX, Prosigna and IHC4+C) in the LN0 NPI  $> 3.4$  subgroup, the NHS England Access Scheme Database<sup>183</sup> was used. This selection was made for two reasons: (1) this source is consistent with the source used to inform the baseline chemotherapy probabilities without testing and (2) the EAG considers that this source provides the best reflection of the way in which three-level tumour profiling tests are used in clinical practice in England.
- For the use of the three-level tests (onco*type* DX, Prosigna and IHC4+C) in the LN1–3 subgroup, the Loncaster *et al.*<sup>145</sup> LN+ estimates were selected as this is the only published UK evidence on decision impact that specifically relates to this patient subgroup.
- For the two-level tests (EPclin and MammaPrint), the Bloomfield *et al.*<sup>159</sup> study was selected for use in all three analysis subgroups as this is the only available published UK study that relates to a two-level tumour profiling test. Given the limited UK-based evidence relating to the impact of two-level tests, two additional European studies are explored in the sensitivity analyses.<sup>162,167</sup>

The other sources not selected for inclusion in the EAG base case were included in the sensitivity analyses.

### Adjuvant chemotherapy treatment effect on distant recurrence: onco*type* DX, Prosigna, IHC4+C and EPclin

As noted in *Chapter 2, Chemotherapy benefit: onco*type* DX*, the evidence relating to the predictive benefit of onco*type* DX is limited to two reanalyses of RCTs<sup>50,53</sup> that do not provide consistent conclusions regarding this aspect of the value of the test across the range of analyses reported. Within the base-case analysis, all tests are assumed to be associated with prognostic benefit only (the relative benefit of chemotherapy is assumed to be the same across all test risk classification groups). For the analyses of onco*type* DX, Prosigna, IHC4+C and EPclin, the RR of recurrence for chemotherapy versus no chemotherapy was derived from a meta-analysis reported by the EBCTCG (2012).<sup>185</sup> Based on data presented in the supplementary material (see EBCTCG publication<sup>185</sup> extra web material, page 12, any anthracycline-based regimen vs. no chemotherapy, distant recurrence), the 10-year risk of distant recurrence for chemotherapy and no chemotherapy was estimated by projecting forward the annualised risk of distant metastases (3.3% per year for chemotherapy, 4.6% per year for no chemotherapy). The RR for chemotherapy versus no chemotherapy was then calculated based on the difference between the projected 10-year DMFS probabilities for the two groups: this gives a 10-year RR of 0.76. The same RR was assumed to apply to the LN0 and LN+ subgroups. The impact of assuming higher and lower RRs for distant recurrence are explored in the sensitivity analyses. Further sensitivity analyses were also undertaken to explore the impact of assuming a predictive benefit of chemotherapy associated with onco*type* DX, based on the studies reported by Paik *et al.*<sup>50</sup> (LN0) and Albain *et al.*<sup>53</sup> (LN+). Within the model, this is implemented by applying different RRs to each of the risk classification groups, based on these two studies.

### Adjuvant chemotherapy treatment effect on distant recurrence: MammaPrint

Within the analysis of MammaPrint, the benefit of adjuvant chemotherapy was estimated using data reported within the MINDACT trial publication,<sup>98</sup> rather than from an external source. The 10-year RR of relapse for adjuvant chemotherapy versus no adjuvant chemotherapy was estimated based only on the discordant clinical and genomic risk group data (see *Appendix 8, Table 79*, EAG group labels C, D, E and F), extrapolated beyond the study end point. RRs of chemotherapy versus no chemotherapy were calculated for each of the two discordant groups (clinical low, genomic high, and clinical high, genomic low) based on estimated 10-year DMFS; these were then weighted in accordance with the number of patients in each discordant group. The weighted RR for the discordant populations was estimated to be 0.77. Within the mAOL low-risk and mAOL high-risk subgroups, the RRs of recurrence for each subgroup

were based only on the discordant population relevant to that subgroup (mAOL low-risk RR 0.84, mAOL high-risk RR 0.74). The impact of assuming higher and lower RRs for distant recurrence are explored in the sensitivity analyses.

The RRs of recurrence applied in the EAG base-case analysis and sensitivity analyses are detailed in *Appendix 8, Table 78*.

It should be noted that the model translates 10-year DMFS probabilities (without chemotherapy) into 6-month event probabilities assuming a constant rate. As a RR relates only to the specified time point of the analysis, it is inappropriate to apply this directly to the 6-month probability of recurrence. Instead, the EAG model applies a conversion by (1) estimating the 10-year DMFS probability with chemotherapy based on the 10-year DMFS probability without chemotherapy and the 10-year RR of recurrence for chemotherapy versus no chemotherapy; (2) estimating the HR for the DMFS outcomes at 10 years for chemotherapy versus no chemotherapy, assuming a constant event rate; (3) applying the estimated HR to the 6-month DMFS probability for the no-chemotherapy group; and (4) converting this HR-adjusted 6-month DMFS probability with chemotherapy to a 6-month distant recurrence probability. This approach ensures that the relative distance between the predicted chemotherapy group and the observed no-chemotherapy group is maintained at 10 years.

### Survival following onset of distant metastases

The survival prognosis of patients with distant metastases was based on analysis of complete hospital and community records of 77 women randomly selected from 232 women who had relapsed breast cancer between 2000 and 2005 (Thomas *et al.*<sup>186</sup>). The population included in this study had an average age of 62.3 years and included patients who had originally been diagnosed with LN+ disease (44%) and who were LN0 (56%). Forty-five per cent of women were ER+ and 21% of women were HER2+. Median survival was reported to be 40.1 months following distant recurrence. The 6-month probability of death was estimated by fitting an exponential distribution with a median of 40.1 months; based this approach, the 6-month probability of death following distant recurrence was estimated to be 0.098, assuming a constant rate. The model assumes that the rate of death due to distant metastases is constant across the different model subgroups and across each test risk classification group owing to a lack of population-specific or risk-group-specific data.

### Probability of local recurrence

The model assumes that 10.5% of patients entering the distant recurrence health state have previously experienced a local recurrence. This estimate was based on a study by de Bock *et al.*,<sup>187</sup> which analysed 3601 women enrolled in three EORTC (European Organisation for Research and Treatment of Cancer) trials. The study included both LN0 and LN+ women who had been treated for early-stage breast cancer. Of the 1224 women who developed distant metastases, 129 women (10.54%) experienced a previous locoregional recurrence. The model does not take into account the time spent alive with local recurrence; instead, the impact of local recurrence is applied crudely in the model as a once-only cost and QALY loss.

### Probability of developing acute myeloid leukaemia

The probability of developing AML following chemotherapy was taken from an analysis of 20,063 patients with stage I–III breast cancer treated at US academic centres between 1998 and 2007 (Wolff *et al.*<sup>188</sup>). Within the cohort of 3227 patients, the estimated 10-year risk of developing AML was reported to be 0.49%. The 6-month probability of developing AML was estimated to be 0.00025, assuming a constant event rate.

### Survival following onset of acute myeloid leukaemia

Survival following the onset of AML was estimated from the NICE single technology appraisal of azacitidine (Vidaza®, Celgene) for myelodysplastic syndromes (MDSs).<sup>202</sup> Within this appraisal, the manufacturer estimated mean survival following the onset of AML to be approximately 8 months; assuming a constant event rate, this gives a 6-month probability of death following AML of 0.53.

### Health utilities associated with relapse-free and distant metastases

Systematic searches were undertaken to identify studies reporting on HRQoL associated with different health states for women with breast cancer. Searches were undertaken in July 2017 in the following electronic databases:

- MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations (Ovid, 1946 to present)
- EMBASE (Ovid, 1974 to 7 July 2017)
- Science Citation Index Expanded (Web of Science, 1900 to present)
- Conference Proceedings Citation Index – Science (Web of Science, 1990 to present).

The searches specifically focused on studies that reported HRQoL estimates for health states that were measured and valued using the Euroqol 5-Dimensions (EQ-5D). The search strategy comprised sensitive MeSH or Emtree Thesauri terms and free-text synonyms for 'breast cancer' combined with free-text synonyms for 'EQ-5D'. The search strategies are presented in *Appendix 2*. Studies were considered potentially relevant if they reported EQ-5D valuations in patients both with non-metastatic disease and with relapsed disease, thereby reflecting key health states in the model. Studies that reported disutilities associated with AEs resulting from the use of chemotherapy were retained for separate consideration. Studies were sifted in accordance with their titles and abstracts; full texts were retrieved for studies that potentially met the inclusion criteria on the basis of the information provided in their title and abstract. HRQoL estimates for other modelled health states and events were not based on new searches; instead, these were derived through consideration of estimates that have been identified from a previous systematic review of health utilities (Peasgood *et al.*<sup>203</sup>).

The EAG's searches identified a total of 227 studies. Of these, only four studies reported EQ-5D valuations for both non-metastatic and metastatic breast cancer states (see *Appendix 8, Table 83*). Three of the identified studies were reported as full papers, and the fourth study was reported only in abstract form. None of the identified studies were undertaken with UK patients: the studies were undertaken in Finland (Farkkila *et al.*<sup>204</sup>), Sweden (Lidgren *et al.*<sup>191</sup>), Iran (Yousefi *et al.*<sup>205</sup>) and Canada (Naik *et al.*<sup>206</sup>).

The study reported by Lidgren *et al.*<sup>191</sup> was selected for use in the EAG base-case analysis on the basis that this population was most likely to best reflect the population of ER+ women with breast cancer who are treated in England. This study reported values for the recurrence-free (receiving endocrine therapy) health state and for the distant recurrence health state of 0.824 and 0.685, respectively. This same study was used to inform the health state utility estimates within the earlier model reported by Ward *et al.*<sup>1</sup> and the Myriad model.<sup>182</sup>

### Health utilities associated with other model health states and events

The disutility associated with local recurrence was taken from a published model of first-, second- and third-generation adjuvant chemotherapy regimens for breast cancer reported by Campbell *et al.*<sup>193</sup> Within this study, the 6-month disutility associated with local recurrence was estimated to be 0.108 [standard error (SE) 0.04]. The HRQoL impact of chemotherapy-related AEs was also taken from Campbell *et al.*;<sup>193</sup> the model assumes a disutility of 0.04 (assumed SE 0.004) during the first 6-month model cycle. The health utility associated with AML was assumed to be 0.26 based on a previous economic evaluation.<sup>192</sup>

### Health utility estimates applied in the External Assessment Group model

*Appendix 8, Table 84*, summarises the health utilities assumed in the EAG's base-case analysis.

## Resource use and costs

The model includes the following cost components:

- costs associated with the tumour profiling test
- costs of adjuvant chemotherapy acquisition and administration (including chemotherapy-related toxicity)
- costs associated with endocrine therapy
- costs of routine follow-up visits and tests
- costs of other therapies (zoledronic acid and G-CSF)
- costs of treating local recurrence (once-only cost)
- costs associated with treating distant metastases.

## Test costs

The costs of the tumour profiling tests were sourced from information provided to NICE by the manufacturers as part of the appraisal process. The cost of *oncoType* DX includes the price discount offered through the Patient Access Scheme (PAS) for this product. The manufacturers of *oncoType* DX, MammaPrint and EndoPredict submitted a cost for sample testing in each of their centralised laboratories. IHC4 and Prosigna have no established centralised laboratory system. The manufacturers provided prices for conducting these two tests in NHS laboratories, as outlined in *Appendix 8, Table 85*. NanoString Technologies submitted a cost of £1970; this is in line with the £1596 (2013 prices) cost of the Prosigna test estimated as part of the OPTIMA Prelim trial.<sup>207</sup> EndoPredict can also be conducted within a NHS laboratory; the impact of assuming a lower cost is considered within the sensitivity analyses. During the course of the appraisal, access proposals were offered by several of the test manufacturers; the impact of these proposals is not included in this report.

## Costs of adjuvant chemotherapy acquisition and administration (including toxicity)

The costs associated with adjuvant chemotherapy were obtained from a previous costing analysis undertaken to inform the economic analysis of the OPTIMA Prelim trial (Hall *et al.*,<sup>30</sup> see *Appendix 8, Table 86*). The fully executable spreadsheet developed to inform the OPTIMA Prelim analysis was made available to the EAG by the study authors (Professor Robert Stein, University College London, personal communication). Within this analysis, standard supportive medication, procurement, laboratory, pharmacy and administration costs were taken from the drugs and pharmaceutical electronic market information tool,<sup>208</sup> the *British National Formulary* (BNF)<sup>194</sup> and *NHS Reference Costs 2013 to 2014*.<sup>209</sup> Unit costs associated with the management of chemotherapy-related grade 3/4 toxicity were based on *NHS Reference Costs 2013 to 2014*.<sup>209</sup> Within the original costing analysis, all costs were valued at 2013/14 prices; within the EAG analysis, these costs were uplifted to current values using the Hospital and Community Health Service (HCHS) indices.<sup>195</sup> The EAG model assumes that women with ER+, HER2-, early-stage breast cancer with zero to three nodes typically receive one of four adjuvant chemotherapy regimens:

1. fluorouracil, epirubicin, cyclophosphamide and docetaxel (FEC100-T) (three plus three cycles, assumed to be given to 25% of patients)
2. docetaxel and cyclophosphamide (TC) (four cycles, assumed to be given to 20% of patients)
3. fluorouracil, epirubicin and cyclophosphamide (FEC75) (six cycles, assumed to be given to 45% of patients)
4. fluorouracil, epirubicin, cyclophosphamide and weekly paclitaxel (FEC100-Pw) (three plus three cycles, assumed to be given to 10% of patients).

The weighted mean cost of adjuvant chemotherapy acquisition, delivery and toxicity was estimated to be £3145.19 per course. All adjuvant chemotherapy costs are applied during the first model cycle. The EAG notes that the choice and proportionate use of alternative chemotherapy regimens may differ between centres; for this reason, the use of alternative chemotherapy cost assumptions are explored in the sensitivity analyses.

### Costs of endocrine therapy

The model assumes that all surviving patients receive endocrine therapy for a period of between 5 and 8 years. The costs associated with endocrine therapy were based on the assumptions employed within the previous economic analysis reported by Ward *et al.*<sup>1</sup> The model assumes that patients may receive one of four endocrine therapy regimens: (1) tamoxifen for 5 years, (2) anastrozole for 5 years, (3) letrozole for 5 years or (4) tamoxifen for 2 years then exemestane for 3 years. The proportion of patients receiving each regimen was taken from Ward *et al.*<sup>1</sup> (tamoxifen 40% of patients, anastrozole 20% of patients, letrozole 20% of patients, tamoxifen then exemestane 20% of patients; see *Appendix 8, Table 87*). In line with the previous model reported by Ward *et al.*,<sup>1</sup> 10% of patients are assumed to receive extended letrozole for 3 further years (years 6–8).

### Costs of additional treatments (zoledronic acid)

The model assumes that 30% of women with early-stage breast cancer will receive 4 mg of bisphosphonates (zoledronic acid) every 6 months by intravenous infusion for up to 3 years (cost per 36-month course = £58.50). Treatment is assumed to be given in a day-case setting, based on the cost of delivering simple parenteral chemotherapy (unit cost of £199.94, based on *NHS Reference Costs 2015 to 2016*,<sup>196</sup> outpatient, currency code SB12Z).

### Follow-up costs

The model assumes that all patients receive two routine follow-up visits during the first year following surgery, with annual visits thereafter for a period of 5 years. Patients are also assumed to undergo a routine annual mammogram for up to 5 years. The cost of a routine follow-up visit was taken from *NHS Reference Costs 2015 to 2016*<sup>196</sup> (mean cost £162.84, SE £6.48, consultant-led, non-admitted, face-to-face attendance, follow-up, medical oncology, service code 370). The cost of a mammogram was not available within the *NHS Reference Costs 2015 to 2016* tariff: this unit cost was instead taken from Campbell *et al.*<sup>193</sup> (mean cost £46.37, SE £9.27) and uplifted to current values using the HCHS index.<sup>195</sup>

### Costs of treatments for local and distant recurrence

The costs associated with treating local recurrence were taken from a UK-based patient-level costing analysis of breast cancer recurrence reported by Karnon *et al.*<sup>197</sup> This cost estimate was uplifted to current prices using the HCHS index<sup>195</sup> (uplifted mean cost £13,912.92, assumed SE £2010.20). This is applied as a once-only cost on the incidence of distant recurrence.

The costs associated with treating distant metastases were derived from the study reported by Thomas *et al.*<sup>186</sup> These costs included costs associated with visits, drugs, pharmacy, hospital admission and intervention, imaging, radiotherapy, pathology and transport. Cost components specifically associated with terminal care were excluded. The 6-monthly cost of treating metastatic breast cancer was estimated to be £4082. This estimate was uplifted to current prices using the HCHS index<sup>195</sup> (uplifted mean cost £4541, assumed SE £908.13).

### Methods for model evaluation

The incremental health outcomes and costs of each test versus standard care were evaluated in a pairwise fashion; the cost-effectiveness of each test was not compared against the other tests. Central estimates of cost-effectiveness were based on the expectation of the mean. Uncertainty was evaluated using probabilistic sensitivity analysis (PSA) and deterministic sensitivity analyses (DSAs). PSA was undertaken using simple Monte Carlo sampling methods (10,000 samples). The choice of distribution assumed for each group of parameters in the model is summarised in *Table 36*. The results of the PSA are presented as cost-effectiveness acceptability curves (CEACs) and in tabular form. DSAs were undertaken to explore the impact of alternative assumptions and evidence sources regarding the probability of receiving chemotherapy with and without the tests, risk classification probabilities, recurrence rates, the potential predictive benefit of *oncoType DX*, the magnitude of chemotherapy benefit, HRQoL estimates and costs.

**TABLE 36** Distributions used in EAG probabilistic analyses

Model parameter group	Distribution	EAG comments
Classification probabilities with/without test	Dirichlet	–
Chemotherapy use (conditional on test result)	Beta	–
Recurrence rates (conditional on test result)	Beta	Distribution parameters fitted to 95% CI around 10-year RFS data from TransATAC <sup>46</sup> or based on number of patients in treatment/risk group in MINDACT <sup>98</sup>
RR chemotherapy vs. no chemotherapy	Log-normal	SE assumed
Distant recurrence risk taper parameters	Fixed	–
OS rate following distant recurrence	Beta	SE estimated using 95% CI of Kaplan–Meier curve in Thomas <i>et al.</i> <sup>186</sup>
Probability of local recurrence	Beta	–
Probability of AML	Beta	–
OS rate following incidence of AML	Beta	–
HRQoL	Beta	–
Chemotherapy costs	Normal	SE assumed to reflect uncertainty in delivery costs only
Endocrine therapy costs	Fixed	–
Zoledronic acid costs	Normal	SE for delivery costs estimated from <i>NHS Reference Costs 2015 to 2016</i> <sup>196</sup> using interquartile ranges and number of submissions
Mammogram costs	Normal	SE taken from Campbell <i>et al.</i> <sup>193</sup>
Follow-up/visit costs	Normal	SE estimated from <i>NHS Reference Costs 2015 to 2016</i> <sup>196</sup> using interquartile range and number of submissions
Local recurrence cost	Normal	SE assumed to be equal to 20% of mean
Distant recurrence cost	Normal	SE assumed to be equal to 20% of mean
AML cost (one off)	Normal	SE assumed to be equal to 20% of mean
Test costs	Fixed	–

The model was subjected to a number of DSAs, which are listed in *Table 37*.

### Model verification and validation

The EAG undertook a number of measures to ensure the credibility of the model:

- peer review of the economic analysis by a modeller not involved in the assessment
- verification and scrutiny of the executable model by two model developers
- double-programming of the deterministic version of the model for all pairwise comparisons presented in the EAG base case
- double-checking of the accuracy of all model inputs against sources
- comparison of model results using point estimates of parameters and the expectation of the mean
- comparison of mean of all probabilistic parameter samples against point estimates of parameters
- examination of all identified sources of discrepancy
- model testing using sensitivity analysis and use of extreme parameter values.

TABLE 37 List of DSAs undertaken for each test

DSA description	DSA undertaken for test?				
	Oncotype DX	IHC4+C	Prosigna	EPClin	MammaPrint
Deterministic base-case analysis	Yes	Yes	Yes	Yes	Yes
Post-test chemotherapy probabilities based on NHS England Access Scheme Database <sup>183</sup> (clinical intermediate risk) (see <i>Appendix 8, Table 82</i> )	Yes	Yes	Yes	No	No
Post-test chemotherapy probabilities based on Holt <i>et al.</i> <sup>201</sup> (see <i>Appendix 8, Table 82</i> )	Yes	Yes	Yes	No	No
Post-test chemotherapy probabilities based on Loncaster <i>et al.</i> <sup>145</sup> (see <i>Appendix 8, Table 82</i> )	Yes	Yes	Yes	No	No
Post-test chemotherapy probabilities based on UKBCG survey (see <i>Appendix 8, Table 82</i> )	Yes	Yes	Yes	Yes	Yes
Post-test chemotherapy probabilities based on NHS England Access Scheme Database <sup>183</sup> (see <i>Appendix 8, Table 83</i> ); baseline chemotherapy probabilities from NCRAS <sup>184</sup> (see <i>Appendix 8, Table 81</i> )	Yes	Yes	Yes	No	No
Post-test chemotherapy probabilities based on Holt <i>et al.</i> <sup>201</sup> (see <i>Appendix 8, Table 83</i> ); baseline chemotherapy probabilities from NCRAS <sup>184</sup> (see <i>Appendix 8, Table 81</i> )	Yes	Yes	Yes	No	No
Post-test chemotherapy probabilities based on Loncaster <i>et al.</i> <sup>145</sup> (see <i>Appendix 8, Table 83</i> ); baseline chemotherapy probabilities from NCRAS <sup>184</sup> (see <i>Appendix 8, Table 81</i> )	Yes	Yes	Yes	No	No
Post-test chemotherapy probabilities based on UKBCG survey (see <i>Appendix 8, Table 83</i> ); baseline chemotherapy probabilities from NCRAS <sup>184</sup> (see <i>Appendix 8, Table 81</i> )	Yes	Yes	Yes	No	No
Post-test chemotherapy probabilities based on Cusumano <i>et al.</i> <sup>167</sup> (see <i>Appendix 8, Table 89</i> )	No	No	No	Yes	Yes
Post-test chemotherapy probabilities based on Penault-Llorca <i>et al.</i> <sup>162</sup> (LN0 only, NPI > 3.4 assumed) (see <i>Appendix 8, Table 90</i> )	No	No	No	Yes	Yes
Baseline chemotherapy probabilities adjusted by oncoprote DX risk score (see <i>Appendix 8, Table 91</i> )	Yes	No	No	No	No
Chemotherapy assumptions (with and without test) based on Ward <i>et al.</i> <sup>1</sup> (LN0, NPI > 3.4 only)	Yes	Yes	Yes	No	No
Oncoprote DX benefit assumed to be associated with predictive benefit. (LN0 RRs based on Paik <i>et al.</i> <sup>50</sup> – low risk 1.31, intermediate risk 0.61, high risk 0.26; LN+ RRs based on Albain <i>et al.</i> <sup>53</sup> – low risk 1.02, intermediate risk 0.72, high risk 0.59)	Yes	No	No	No	No
Risk classification and distant metastases probabilities based on oncoprote DX RPSC <sup>46</sup> (LN0 only) (see <i>Appendix 8, Table 92</i> )	Yes	No	No	No	No
Prosigna risk classification and distant metastases probabilities derived from Gnant <i>et al.</i> <sup>104</sup> (LN+ only) (see <i>Appendix 8, Table 93</i> )	No	No	Yes	No	No
EPClin risk classification and distant metastases probabilities derived from Dubsy <i>et al.</i> <sup>120</sup> (LN+ only) (see <i>Appendix 8, Table 94</i> )	No	No	No	Yes	No
MammaPrint risk classification and distant metastases probabilities derived from van 't Veer <i>et al.</i> <sup>91</sup> (LN0 only) (see <i>Appendix 8, Table 95</i> )	No	No	No	No	Yes
Subgroup analysis in ER+, HER2-, LN+ subgroup	No	No	No	No	Yes
Assume MammaPrint low-risk patients receive no chemotherapy, MammaPrint high-risk patients receive 100% chemotherapy	No	No	No	No	Yes

continued

**TABLE 37** List of DSAs undertaken for each test (*continued*)

DSA description	DSA undertaken for test?				
	Oncotype DX	IHC4+C	Prosigna	EPclin	MammaPrint
10% lower cost per test owing to increased efficiency (local NHS testing)	No	No	Yes	Yes	No
10% higher cost per test owing to decreased efficiency (local NHS testing)	No	No	Yes	No	No
Baseline chemotherapy use halved	No	No	No	No	Yes
Start age based on TransATAC <sup>37</sup> (64 years)	Yes	Yes	Yes	Yes	Yes
RR of distant metastases for chemotherapy vs. no chemotherapy = 0.70	Yes	Yes	Yes	Yes	Yes
RR of distant metastases for chemotherapy vs. no chemotherapy = 0.80	Yes	Yes	Yes	Yes	Yes
Removal of distant metastases risk tapering	Yes	Yes	Yes	Yes	Yes
Utilities derived from Farkkila <i>et al.</i> <sup>204</sup> (RFS = 0.818, DM = 0.746)	Yes	Yes	Yes	Yes	Yes
Distant metastases death rate doubled	Yes	Yes	Yes	Yes	Yes
Distant metastases death rate halved	Yes	Yes	Yes	Yes	Yes
AML removed from model	Yes	Yes	Yes	Yes	Yes
Chemotherapy cost doubled	Yes	Yes	Yes	Yes	Yes
Chemotherapy cost halved	Yes	Yes	Yes	Yes	Yes
Endocrine therapy costs doubled	Yes	Yes	Yes	Yes	Yes
Endocrine therapy costs halved	Yes	Yes	Yes	Yes	Yes
Local and distant metastases costs doubled	Yes	Yes	Yes	Yes	Yes
Local and distant metastases costs halved	Yes	Yes	Yes	Yes	Yes

DM, distant metastasis; RFS, recurrence-free survival.

### Cost-effectiveness results

#### Oncotype DX versus current practice

##### Central estimates of cost-effectiveness: probabilistic

Central estimates of cost-effectiveness for *oncotype* DX versus current practice are presented in *Table 38*. All estimates are based on the probabilistic version of the EAG model. Within the LN0 NPI ≤ 3.4 subgroup, *oncotype* DX is expected to produce 0.01 additional QALYs at an additional cost of £1313 per woman tested compared with current practice; this corresponds to an incremental cost-effectiveness ratio (ICER) of £122,725 per QALY gained. Within the LN0 NPI > 3.4 subgroup, *oncotype* DX is expected to produce 0.01 fewer QALYs at an additional cost of £881 per woman tested compared with current practice; within this subgroup, *oncotype* DX is expected to be dominated. Within the LN1–3 subgroup, *oncotype* DX is expected to produce 0.07 fewer QALYs at an additional cost of £687 per woman tested compared with current practice; within this subgroup, *oncotype* DX is, again, expected to be dominated. As shown in *Table 39*, the PSA indicates that the probability that *oncotype* DX produces more net benefit than current practice at willingness-to-pay (WTP) thresholds of £20,000 and £30,000 per QALY gained is ≤ 0.04 across all three subgroups. The results for the LN0 NPI > 3.4 subgroup and the LN1–3 subgroup are primarily driven by the lower use of chemotherapy (and the benefits forgone) with *oncotype* DX than with current practice (see *Appendix 10* for the impact of all tests).

**TABLE 38** Central estimates of cost-effectiveness: oncotype DX vs. current practice – probabilistic model

Option	QALYs	Costs	Incremental QALYs	Incremental costs	ICER (per QALY gained)
<b>LN0 NPI ≤ 3.4</b>					
Oncotype DX	13.89	£5474	0.01	£1313	£122,725
No test	13.88	£4161	–	–	–
<b>LN0 NPI &gt; 3.4</b>					
Oncotype DX	12.73	£11,806	–0.01	£881	Dominated
No test	12.74	£10,925	–	–	–
<b>LN1–3</b>					
Oncotype DX	12.48	£13,212	–0.07	£687	Dominated
No test	12.55	£12,525	–	–	–

**TABLE 39** Probability of optimality: oncotype DX vs. current practice

Subgroup	Probability ( $\lambda = \text{£}20,000$ per QALY gained)		Probability ( $\lambda = \text{£}30,000$ per QALY gained)	
	Oncotype DX	Current practice	Oncotype DX	Current practice
LN0 NPI ≤ 3.4	0.00	1.00	0.00	1.00
LN0 NPI > 3.4	0.01	0.99	0.04	0.96
LN1–3	0.00	1.00	0.01	0.99

### Deterministic sensitivity analysis

The results of the DSAs for oncotype DX are presented in *Table 40* (shaded cells reflect analyses that are unchanged from the EAG's base case). The DSAs indicate the following results across the three subgroups:

- LN0 NPI ≤ 3.4 – the ICER for oncotype DX versus current practice remains in excess of £34,000 per QALY gained across all scenarios. The only analysis in which the ICER is < £70,000 per QALY gained relates to the scenario in which oncotype DX is assumed to be predictive of chemotherapy benefit, based on RRs reported by Paik *et al.*<sup>50</sup>
- LN0 NPI > 3.4 – oncotype DX is either dominated or has an ICER in excess of £35,000 per QALY gained across almost all scenarios. The only exception is the scenario in which oncotype DX is assumed to be predictive of chemotherapy benefit, based on RRs reported by Paik *et al.*<sup>50</sup> Within this analysis, oncotype DX dominates current practice.
- LN1–3 – oncotype DX remains dominated across the majority of scenarios tested. The exceptions are (1) the scenario in which oncotype DX is assumed to be predictive of chemotherapy benefit, based on treatment effect estimates reported by Albain *et al.*,<sup>53</sup> and (2) the scenario in which the cost of adjuvant chemotherapy is doubled.

**TABLE 40** Deterministic sensitivity analyses: oncotype DX vs. current practice

Scenario	Subgroup								
	LN0 NPI ≤ 3.4			LN0 NPI > 3.4			LN1-3		
	Incremental QALYs	Incremental costs	ICER	Incremental QALYs	Incremental costs	ICER	Incremental QALYs	Incremental costs	ICER
Base case (deterministic)	0.01	£1317	£120,144	-0.02	£869	Dominated	-0.07	£647	Dominated
LN0 NPI ≤ 3.4 post-test P(chemotherapy) (NHSE <sup>183</sup> )	0.01	£1458	£117,326	-0.02	£869	Dominated	-0.07	£647	Dominated
LN0 NPI ≤ 3.4 post-test P(chemotherapy) (Holt <i>et al.</i> <sup>141</sup> )	0.01	£1849	£173,680	-0.02	£869	Dominated	-0.07	£647	Dominated
LN0 NPI ≤ 3.4 post-test P(chemotherapy) (Loncaster <i>et al.</i> <sup>145</sup> )	0.01	£1640	£129,527	-0.02	£869	Dominated	-0.07	£647	Dominated
LN0 NPI > 3.4 post-test P(chemotherapy) (Holt <i>et al.</i> <sup>141</sup> )	0.01	£1317	£120,144	0.02	£1138	£60,831	-0.07	£647	Dominated
LN0 NPI > 3.4 post-test P(chemotherapy) (Loncaster <i>et al.</i> <sup>145</sup> )	0.01	£1317	£120,144	0.00	£999	£651,857	-0.07	£647	Dominated
LN0 NPI > 3.4 post-test P(chemotherapy) (UKBCG survey)	0.01	£1317	£120,144	0.00	£978	Dominated	-0.07	£647	Dominated
LN0 NPI > 3.4 baseline P(chemotherapy) (NCRAS <sup>184</sup> ), post-test P(chemotherapy) (Holt <i>et al.</i> <sup>141</sup> )	0.01	£1317	£120,144	0.03	£1207	£44,817	-0.07	£647	Dominated
LN0 NPI > 3.4 baseline P(chemotherapy) (NCRAS <sup>184</sup> ), post-test P(chemotherapy) (Loncaster <i>et al.</i> <sup>145</sup> LN0 subgroup)	0.01	£1317	£120,144	0.01	£1069	£109,429	-0.07	£647	Dominated
LN0 NPI > 3.4 baseline P(chemotherapy) (NCRAS <sup>184</sup> ), post-test P(chemotherapy) (UKBCG survey)	0.01	£1317	£120,144	0.01	£1048	£161,535	-0.07	£647	Dominated
LN+ post-test P(chemotherapy) (UKBCG survey)	0.01	£1317	£120,144	-0.02	£869	Dominated	0.00	£1155	Dominated

Scenario	Subgroup								
	LN0 NPI ≤ 3.4			LN0 NPI > 3.4			LN1–3		
	Incremental QALYs	Incremental costs	ICER	Incremental QALYs	Incremental costs	ICER	Incremental QALYs	Incremental costs	ICER
Baseline P(chemotherapy) adjusted by onco $\text{type}$ DX RS	0.01	£1317	£120,144	–0.02	£888	Dominated	–0.07	£647	Dominated
Ward <i>et al.</i> <sup>1</sup> scenario: baseline P(chemotherapy) WMCIU <sup>1</sup> , post-test P(chemotherapy) (Holt <i>et al.</i> <sup>141</sup> )	0.01	£1317	£120,144	0.04	£1268	£35,782	–0.07	£647	Dominated
Oncotype DX predictive benefit	0.04	£1211	£34,245	0.27	–£364	Dominating	0.09	–£68	Dominating
Oncotype DX RSPC LN0	0.02	£1146	£70,435	–0.02	£847	Dominated	–0.07	£647	Dominated
Chemotherapy disutility doubled	0.01	£1317	£121,879	–0.01	£869	Dominated	–0.06	£647	Dominated
Chemotherapy disutility halved	0.01	£1317	£119,294	–0.02	£869	Dominated	–0.08	£647	Dominated
Start age based on TransATAC <sup>38,46</sup> (64 years)	0.01	£1319	£156,971	–0.01	£867	Dominated	–0.05	£638	Dominated
Farkkila <i>et al.</i> <sup>204</sup> utilities (RFS = 0.818, DM = 0.746)	0.01	£1317	£125,021	–0.01	£869	Dominated	–0.07	£647	Dominated
Chemotherapy RR = 0.70	0.01	£1305	£94,920	–0.02	£905	Dominated	–0.10	£759	Dominated
Chemotherapy RR = 0.80	0.01	£1325	£145,102	–0.01	£845	Dominated	–0.05	£573	Dominated
No risk tapering	0.01	£1292	£92,613	–0.03	£974	Dominated	–0.10	£870	Dominated
Distant metastases death rate doubled	0.01	£1339	£106,090	–0.02	£803	Dominated	–0.09	£443	Dominated
Distant metastases death rate halved	0.01	£1282	£154,090	–0.01	£974	Dominated	–0.05	£972	Dominated
AML removed	0.01	£1318	£119,771	–0.03	£879	Dominated	–0.09	£663	Dominated
Chemotherapy cost doubled	0.01	£1330	£121,322	–0.02	£374	Dominated	–0.07	–£266	£3700

continued

**TABLE 40** Deterministic sensitivity analyses: oncotype DX vs. current practice (*continued*)

Scenario	Subgroup								
	LN0 NPI ≤ 3.4			LN0 NPI > 3.4			LN1–3		
	Incremental QALYs	Incremental costs	ICER	Incremental QALYs	Incremental costs	ICER	Incremental QALYs	Incremental costs	ICER
Chemotherapy cost halved	0.01	£1311	£119,554	–0.02	£1116	Dominated	–0.07	£1103	Dominated
Endocrine therapy costs doubled	0.01	£1317	£120,149	–0.02	£869	Dominated	–0.07	£646	Dominated
Endocrine therapy costs halved	0.01	£1317	£120,141	–0.02	£869	Dominated	–0.07	£647	Dominated
Local and distant recurrence costs doubled	0.01	£1268	£115,630	–0.02	£1017	Dominated	–0.07	£1106	Dominated
Local and distant recurrence costs halved	0.01	£1342	£122,400	–0.02	£795	Dominated	–0.07	£417	Dominated

DM, distant metastasis; NHSE, NHS England; P(chemotherapy), probability of receiving chemotherapy; RFS, recurrence-free survival; RS, recurrence score; WMCIU, West Midlands Cancer Intelligence Unit.

**Note**  
Shaded cells reflect analyses that are unchanged from the EAG's base case.

## IHC4+C versus current practice

**Central estimates of cost-effectiveness: probabilistic**

Central estimates of cost-effectiveness for IHC4+C versus current practice are presented in *Table 41*. All estimates are based on the probabilistic version of the EAG model. Within the LN0 NPI  $\leq 3.4$  subgroup, IHC4+C is expected to produce 0.01 additional QALYs at an additional cost of £22 per woman tested compared with current practice; this corresponds to an ICER of £2654 per QALY gained. Within the LN0 NPI  $> 3.4$  subgroup, IHC4+C is expected to produce 0.01 additional QALYs and cost savings of £90 per woman tested compared with current practice; within this subgroup, IHC4+C is expected to dominate current practice. Within the LN1–3 subgroup, IHC4+C is expected to produce 0.05 additional QALYs and cost savings of £287 per woman tested compared with current practice; within this subgroup, IHC4+C is expected to dominate current practice. As shown in *Table 42*, the PSA indicates that within the LN0 NPI  $\leq 3.4$  subgroup, the probability that IHC4+C produces more net benefit than current practice at WTP thresholds of £20,000 and £30,000 per QALY gained is 0.95 and 0.97, respectively. Within the LN0 NPI  $> 3.4$  subgroup, the probability that IHC4+C produces more net benefit than current practice at WTP thresholds of £20,000 and £30,000 per QALY gained is 0.69 and 0.67, respectively. Within the LN1–3 subgroup, the probability that IHC4+C produces more net benefit than current practice at these WTP thresholds is  $\geq 0.94$ .

**TABLE 41** Central estimates of cost-effectiveness: IHC4+C vs. current practice – probabilistic model

Option	QALYs	Costs	Incremental QALYs	Incremental costs	ICER (per QALY gained)
<b>LN0 NPI <math>\leq 3.4</math></b>					
IHC4+C	13.86	£4291	0.01	£22	£2654
No test	13.86	£4269	–	–	–
<b>LN0 NPI <math>&gt; 3.4</math></b>					
IHC4+C	12.73	£10,941	0.01	–£90	Dominating
No test	12.72	£11,031	–	–	–
<b>LN1–3</b>					
IHC4+C	12.59	£12,268	0.05	–£287	Dominating
No test	12.54	£12,554	–	–	–

**TABLE 42** Probability of optimality: IHC4+C vs. current practice

Subgroup	Probability ( $\lambda = £20,000$ per QALY gained)		Probability ( $\lambda = £30,000$ per QALY gained)	
	IHC4+C	Current practice	IHC4+C	Current practice
LN0 NPI $\leq 3.4$	0.95	0.05	0.97	0.03
LN0 NPI $> 3.4$	0.69	0.31	0.67	0.33
LN1–3	0.95	0.05	0.94	0.06

**Deterministic sensitivity analysis**

The results of the DSAs for IHC4+C are presented in *Table 43* (shaded cells reflect analyses that are unchanged from the EAG's base case). The DSAs indicate the following:

- LN0 NPI  $\leq 3.4$  – the ICER for IHC4+C versus current practice remains below £16,000 per QALY gained across all scenarios, except in the analysis in which post-test chemotherapy probabilities are derived from Holt *et al.*<sup>201</sup> IHC4+C dominates current practice in the scenario in which the cost of adjuvant chemotherapy is doubled.
- LN0 NPI  $> 3.4$  – IHC4+C dominates current practice or has an ICER of  $< \text{£}6000$  per QALY gained across all scenarios.
- LN1–3 – IHC4+C dominates current practice across all scenarios except the analysis in which the probability of receiving chemotherapy conditional on IHC4+C risk level is based on the UKBCG survey; within this analysis, the ICER is estimated to be £1929 per QALY gained.

**Prosigna versus current practice****Central estimates of cost-effectiveness: probabilistic**

Central estimates of cost-effectiveness for Prosigna versus current practice are presented in *Table 44*. All estimates are based on the probabilistic version of the EAG model. Within the LN0 NPI  $\leq 3.4$  subgroup, Prosigna is expected to produce 0.02 additional QALYs at an additional cost of £1884 per woman tested compared with current practice; this corresponds to an ICER of £91,028 per QALY gained. Within the LN0 NPI  $> 3.4$  subgroup, Prosigna is expected to produce 0.06 additional QALYs at an additional cost of £1686 per woman tested compared with current practice; the corresponding ICER is £26,058 per QALY gained. Within the LN1–3 subgroup, Prosigna is expected to produce 0.07 additional QALYs at an additional cost of £1936 per woman tested compared with current practice; the corresponding ICER is £28,731 per QALY gained. As shown in *Table 45*, the PSA indicates that within the LN0 NPI  $\leq 3.4$  subgroup, the probability that Prosigna produces more net benefit than current practice at WTP thresholds of £20,000 and £30,000 per QALY gained is approximately zero. Within the LN0 NPI  $> 3.4$  subgroup, the probabilities that Prosigna produces more net benefit than current practice at these WTP thresholds are 0.24 and 0.60, respectively. Within the LN1–3 subgroup, the probabilities that Prosigna produces more net benefit than current practice at these WTP thresholds are 0.24 and 0.55, respectively.

**Deterministic sensitivity analysis**

The results of the DSAs for Prosigna are presented in *Table 46* (shaded cells reflect analyses that are unchanged from the EAG's base case). The DSAs indicate the following:

- LN0 NPI  $\leq 3.4$  – the ICER for Prosigna versus current practice is estimated to be  $> \text{£}71,000$  per QALY gained across all scenarios.
- LN0 NPI  $> 3.4$  – the ICER for Prosigna versus current practice is estimated to be  $< \text{£}30,000$  per QALY gained across most scenarios. The DSAs indicate that the ICER for Prosigna versus current practice is  $> \text{£}30,000$  per QALY gained for scenarios in which (1) an older start age is assumed and (2) the RR of distant metastases for chemotherapy versus no chemotherapy is set equal to 0.80.
- LN1–3 – the ICER for Prosigna versus current practice is estimated to be consistently below £38,000 per QALY gained across all analyses. Less favourable ICERs were estimated for scenarios in which (1) the disutility associated with chemotherapy-related AEs is doubled, (2) an older cohort age is assumed, (3) the RR of distant metastases for chemotherapy versus no chemotherapy is set equal to 0.80, (4) the cost of chemotherapy is doubled, (5) the costs of treating local and distant recurrence are halved, (6) the mortality rate for distant metastases is halved and (7) the cost per test is assumed to be increased owing to lower efficiency. The analysis in which risk classification probabilities and associated DMFS probabilities were taken from Gnant *et al.*<sup>104</sup> was not evaluable as no events occurred at 10 years within the low-risk Prosigna category.

**TABLE 43** Deterministic sensitivity analyses: IHC4+C vs. current practice

Scenario	Subgroup								
	LN0 NPI ≤ 3.4			LN0 NPI > 3.4			LN1–3		
	Incremental QALYs	Incremental costs	ICER	Incremental QALYs	Incremental costs	ICER	Incremental QALYs	Incremental costs	ICER
Base case (deterministic)	0.01	£22.43	£2752	0.01	–£89.12	Dominating	0.05	–£269.39	Dominating
LN0 NPI ≤ 3.4 post-test P(chemotherapy) (NHSE <sup>183</sup> )	0.01	£94.18	£9265	0.01	–£89.12	Dominating	0.05	–£269.39	Dominating
LN0 NPI ≤ 3.4 post-test P(chemotherapy) (Holt <i>et al.</i> <sup>141</sup> )	0.01	£390.39	£36,259	0.01	–£89.12	Dominating	0.05	–£269.39	Dominating
LN0 NPI ≤ 3.4 post-test P(chemotherapy) (Loncaster <i>et al.</i> <sup>145</sup> )	0.01	£195.20	£15,875	0.01	–£89.12	Dominating	0.05	–£269.39	Dominating
LN0 NPI > 3.4 post-test P(chemotherapy) (Holt <i>et al.</i> <sup>141</sup> )	0.01	£22.43	£2752	0.05	£194.16	£4147	0.05	–£269.39	Dominating
LN0 NPI > 3.4 post-test P(chemotherapy) (Loncaster <i>et al.</i> <sup>145</sup> )	0.01	£22.43	£2752	0.03	£52.99	£1864	0.05	–£269.39	Dominating
LN0 NPI > 3.4 post-test P(chemotherapy) (UKBCG survey)	0.01	£22.43	£2752	0.02	£23.00	£1040	0.05	–£269.39	Dominating
LN0 NPI > 3.4 baseline P(chemotherapy) (NCRAS <sup>184</sup> ), post-test P(chemotherapy) (Holt <i>et al.</i> <sup>141</sup> )	0.01	£22.43	£2752	0.06	£262.95	£4760	0.05	–£269.39	Dominating
LN0 NPI > 3.4 baseline P(chemotherapy) (NCRAS <sup>184</sup> ), post-test P(chemotherapy) (Loncaster <i>et al.</i> <sup>145</sup> LN0 subgroup)	0.01	£22.43	£2752	0.04	£121.78	£3305	0.05	–£269.39	Dominating
LN0 NPI > 3.4 baseline P(chemotherapy) (NCRAS <sup>184</sup> ), post-test P(chemotherapy) (UKBCG survey)	0.01	£22.43	£2752	0.03	£91.80	£3005	0.05	–£269.39	Dominating
LN+ post-test P(chemotherapy) (UKBCG survey)	0.01	£22.43	£2752	0.01	–£89.12	Dominating	0.09	£167.12	£1929
Ward <i>et al.</i> <sup>1</sup> scenario: baseline P(chemotherapy) (WMCIU), post-test P(chemotherapy) (Holt <i>et al.</i> <sup>141</sup> )	0.01	£22.43	£2752	0.06	£325.33	£5160	0.05	–£269.39	Dominating

continued

**TABLE 43** Deterministic sensitivity analyses: IHC4+C vs. current practice (*continued*)

Scenario	Subgroup								
	LN0 NPI ≤ 3.4			LN0 NPI > 3.4			LN1–3		
	Incremental QALYs	Incremental costs	ICER	Incremental QALYs	Incremental costs	ICER	Incremental QALYs	Incremental costs	ICER
Chemotherapy disutility doubled	0.01	£22.43	£2304	0.01	–£89.12	Dominating	0.05	–£269.39	Dominating
Chemotherapy disutility halved	0.01	£22.43	£3049	0.01	–£89.12	Dominating	0.05	–£269.39	Dominating
Start age based on TransATAC <sup>38,46</sup> (64 years)	0.01	£23.21	£3542	0.01	–£88.85	Dominating	0.04	–£264.75	Dominating
Farkkila <i>et al.</i> <sup>204</sup> utilities (RFS = 0.818, DM = 0.746)	0.01	£22.43	£2802	0.01	–£89.12	Dominating	0.05	–£269.39	Dominating
Chemotherapy RR = 0.70	0.01	£19.09	£2138	0.01	–£86.90	Dominating	0.06	–£314.00	Dominating
Chemotherapy RR = 0.80	0.01	£24.62	£3223	0.01	–£90.60	Dominating	0.05	–£240.14	Dominating
No risk tapering	0.01	£19.17	£2221	0.00	–£51.24	Dominating	0.06	–£282.61	Dominating
Distant metastases death rate doubled	0.01	£28.48	£3309	0.01	–£93.23	Dominating	0.06	–£188.59	Dominating
Distant metastases death rate halved	0.01	£12.78	£1722	0.01	–£82.69	Dominating	0.04	–£398.33	Dominating
AML removed	0.00	£26.13	£5560	0.00	–£83.05	Dominating	0.04	–£260.08	Dominating
Chemotherapy cost doubled	0.01	–£108.78	Dominating	0.01	–£326.21	Dominating	0.05	–£499.21	Dominating
Chemotherapy cost halved	0.01	£88.03	£10,803	0.01	£29.42	£4056	0.05	–£154.48	Dominating
Endocrine therapy costs doubled	0.01	£22.45	£2755	0.01	–£89.10	Dominating	0.05	–£269.11	Dominating
Endocrine therapy costs halved	0.01	£22.41	£2751	0.01	–£89.14	Dominating	0.05	–£269.53	Dominating
Local and distant recurrence costs doubled	0.01	£8.80	£1079	0.01	–£79.87	Dominating	0.05	–£451.35	Dominating
Local and distant recurrence costs halved	0.01	£29.24	£3588	0.01	–£93.75	Dominating	0.05	–£178.41	Dominating

DM, distant metastasis; NHSE, NHS England; P(chemotherapy), probability of receiving chemotherapy; RFS, recurrence-free survival; WMCIU, West Midlands Cancer Intelligence Unit.

**Note**

Shaded cells reflect analyses that are unchanged from the EAG's base case.

**TABLE 44** Central estimates of cost-effectiveness: Prosigna vs. current practice – probabilistic model

Option	QALYs	Costs	Incremental QALYs	Incremental costs	ICER (per QALY gained)
<b>LNO NPI ≤ 3.4</b>					
Prosigna	13.87	£6201	0.02	£1884	£91,028
No test	13.84	£4318	–	–	–
<b>LNO NPI &gt; 3.4</b>					
Prosigna	12.65	£13,330	0.06	£1686	£26,058
No test	12.59	£11,644	–	–	–
<b>LN1–3</b>					
Prosigna	12.47	£15,172	0.07	£1936	£28,731
No test	12.40	£13,236	–	–	–

**TABLE 45** Probability of optimality: Prosigna vs. current practice

Subgroup	Probability ( $\lambda = £20,000$ per QALY gained)		Probability ( $\lambda = £30,000$ per QALY gained)	
	Prosigna	Current practice	Prosigna	Current practice
LNO NPI ≤ 3.4	0.00	1.00	0.00	1.00
LNO NPI > 3.4	0.24	0.76	0.60	0.40
LN1–3	0.24	0.76	0.55	0.45

## EndoPredict Clinical versus current practice

### Central estimates of cost-effectiveness: probabilistic

Central estimates of cost-effectiveness for EPclin versus current practice are presented in *Table 47*. All estimates are based on the probabilistic version of the EAG model. Within the LNO NPI ≤ 3.4 subgroup, EPclin is expected to produce 0.01 additional QALYs at an additional cost of £1679 per woman tested compared with current practice; this corresponds to an ICER of £147,419 per QALY gained. Within the LNO NPI > 3.4 subgroup, EPclin is expected to produce 0.03 additional QALYs at an additional cost of £1388 per woman tested compared with current practice; the corresponding ICER is £46,788 per QALY gained. Within the LN1–3 subgroup, EPclin is expected to produce 0.05 additional QALYs at an additional cost of £1164 per woman tested compared with current practice; the corresponding ICER is £21,458 per QALY gained. As shown in *Table 48*, the PSA indicates that within the LNO NPI ≤ 3.4 subgroup, the probability that EPclin produces more net benefit than current practice at WTP thresholds of £20,000 and £30,000 per QALY gained is zero. Within the LNO NPI > 3.4 subgroup, the probabilities that EPclin produces more net benefit than current practice at these WTP thresholds are 0.09 and 0.26, respectively. Within the LN1–3 subgroup, the probabilities that EPclin produces more net benefit than current practice at these WTP thresholds are 0.44 and 0.73, respectively.

TABLE 46 Deterministic sensitivity analyses: Prosigna vs. current practice

Scenario	Subgroup								
	LN0 NPI ≤ 3.4			LN0 NPI > 3.4			LN1-3		
	Incremental QALYs	Incremental costs	ICER	Incremental QALYs	Incremental costs	ICER	Incremental QALYs	Incremental costs	ICER
Base case (deterministic)	0.02	£1891.35	£89,693	0.07	£1712.67	£25,857	0.07	£1966.54	£28,666
LN0 NPI ≤ 3.4 post-test P(chemotherapy) (NHSE <sup>183</sup> )	0.02	£2025.87	£84,090	0.07	£1712.67	£25,857	0.07	£1966.54	£28,666
LN0 NPI ≤ 3.4 post-test P(chemotherapy) (Holt <i>et al.</i> <sup>141</sup> )	0.02	£2421.22	£109,620	0.07	£1712.67	£25,857	0.07	£1966.54	£28,666
LN0 NPI ≤ 3.4 post-test P(chemotherapy) (Loncaster <i>et al.</i> <sup>145</sup> )	0.02	£2213.71	£93,938	0.07	£1712.67	£25,857	0.07	£1966.54	£28,666
LN0 NPI > 3.4 post-test P(chemotherapy) (Holt <i>et al.</i> <sup>141</sup> )	0.02	£1891.35	£89,693	0.10	£1991.89	£19,356	0.07	£1966.54	£28,666
LN0 NPI > 3.4 post-test P(chemotherapy) (Loncaster <i>et al.</i> <sup>145</sup> )	0.02	£1891.35	£89,693	0.09	£1993.10	£21,216	0.07	£1966.54	£28,666
LN0 NPI > 3.4 post-test P(chemotherapy) (UKBCG survey)	0.02	£1891.35	£89,693	0.08	£1820.85	£22,420	0.07	£1966.54	£28,666
LN0 NPI > 3.4 baseline P(chemotherapy) (NCRAS <sup>184</sup> ), post-test P(chemotherapy) (Holt <i>et al.</i> <sup>141</sup> )	0.02	£1891.35	£89,693	0.11	£2056.25	£18,288	0.07	£1966.54	£28,666
LN0 NPI > 3.4 baseline P(chemotherapy) (NCRAS <sup>184</sup> ), post-test P(chemotherapy) (Loncaster <i>et al.</i> <sup>145</sup> LN0 subgroup)	0.02	£1891.35	£89,693	0.09	£1922.48	£20,971	0.07	£1966.54	£28,666
LN0 NPI > 3.4 baseline P(chemotherapy) NCRAS <sup>184</sup> , post-test P(chemotherapy) (UKBCG survey)	0.02	£1891.35	£89,693	0.09	£1885.20	£20,774	0.07	£1966.54	£28,666
LN+ post-test P(chemotherapy) (UKBCG survey)	0.02	£1891.35	£89,693	0.07	£1712.67	£25,857	0.11	£2227.53	£20,427
Ward <i>et al.</i> <sup>1</sup> scenario: baseline P(chemotherapy) (WMCIU), post-test P(chemotherapy) (Holt <i>et al.</i> <sup>141</sup> )	0.02	£1891.35	£89,693	0.13	£2109.68	£16,568	0.07	£1966.54	£28,666
Risk classification and DMFS probabilities from Gnant <i>et al.</i> <sup>104</sup> LN+ subgroup	0.02	£1891.35	£89,693	0.07	£1712.67	£25,857	Not evaluable		
10% lower cost per test owing to increased efficiency (local NHS testing)	0.02	£1694.00	£80,348	0.07	£1516	£22,882	0.07	£1769	£25,794

Scenario	Subgroup								
	LN0 NPI ≤ 3.4			LN0 NPI > 3.4			LN1-3		
	Incremental QALYs	Incremental costs	ICER	Incremental QALYs	Incremental costs	ICER	Incremental QALYs	Incremental costs	ICER
10% higher cost per test owing to decreased efficiency (local NHS testing)	0.02	£2088	£99,038	0.07	£1910	£28,832	0.07	£2164	£31,539
Chemotherapy disutility doubled	0.02	£1891.35	£90,123	0.07	£1712.67	£25,935	0.07	£1966.54	£30,026
Chemotherapy disutility halved	0.02	£1891.35	£89,480	0.07	£1712.67	£25,818	0.07	£1966.54	£28,032
Start age based on TransATAC <sup>38,46</sup> (64 years)	0.02	£1893.35	£115,741	0.05	£1718.65	£33,348	0.05	£1973.37	£37,480
Farkkila <i>et al.</i> <sup>204</sup> utilities (RFS = 0.818, DM = 0.746)	0.02	£1891.35	£93,183	0.06	£1712.67	£26,854	0.07	£1966.54	£29,913
Chemotherapy RR = 0.70	0.03	£1869.14	£71,107	0.08	£1643.59	£19,926	0.09	£1884.89	£21,508
Chemotherapy RR = 0.80	0.02	£1905.92	£107,875	0.06	£1757.96	£31,645	0.06	£2020.11	£36,018
No risk tapering	0.02	£1870.73	£78,043	0.07	£1681.49	£23,298	0.08	£1874.66	£23,138
Distant metastases death rate doubled	0.02	£1931.61	£80,059	0.08	£1837.80	£24,281	0.08	£2114.58	£26,505
Distant metastases death rate halved	0.02	£1827.15	£112,523	0.05	£1513.02	£29,575	0.05	£1730.53	£34,081
AML removed	0.02	£1892.76	£91,182	0.06	£1717.28	£26,432	0.07	£1965.75	£26,851
Chemotherapy cost doubled	0.02	£1899.68	£90,088	0.07	£1729.27	£26,107	0.07	£2223.61	£32,414
Chemotherapy cost halved	0.02	£1887.19	£89,496	0.07	£1704.37	£25,731	0.07	£1838.01	£26,793
Endocrine therapy costs doubled	0.02	£1891.48	£89,699	0.07	£1713.06	£25,863	0.07	£1966.96	£28,673
Endocrine therapy costs halved	0.02	£1891.29	£89,690	0.07	£1712.47	£25,854	0.07	£1966.33	£28,663
Local and distant recurrence costs doubled	0.02	£1800.69	£85,393	0.07	£1430.87	£21,602	0.07	£1633.14	£23,806
Local and distant recurrence costs halved	0.02	£1936.69	£91,843	0.07	£1853.57	£27,984	0.07	£2133.24	£31,096

DM, distant metastasis; NHSE, NHS England; P(chemotherapy), probability of receiving chemotherapy; RFS, recurrence-free survival; WMCIU, West Midlands Cancer Intelligence Unit.

**Note**

Shaded cells reflect analyses that are unchanged from the EAG's base case.

**TABLE 47** Central estimates of cost-effectiveness: EPCLin vs. current practice – probabilistic model

Option	QALYs	Costs	Incremental QALYs	Incremental costs	ICER (per QALY gained)
<b>LN0 NPI ≤ 3.4</b>					
EPCLin	13.85	£6034	0.01	£1679	£147,419
No test	13.84	£4355	–	–	–
<b>LN0 NPI &gt; 3.4</b>					
EPCLin	12.71	£12,612	0.03	£1388	£46,788
No test	12.68	£11,224	–	–	–
<b>LN1–3</b>					
EPCLin	12.52	£14,080	0.05	£1164	£21,458
No test	12.46	£12,916	–	–	–

**TABLE 48** Probability of optimality: EPCLin vs. current practice

Subgroup	Probability ( $\lambda = £20,000$ per QALY gained)		Probability ( $\lambda = £30,000$ per QALY gained)	
	EPCLin	Current practice	EPCLin	Current practice
LN0 NPI ≤ 3.4	0.00	1.00	0.00	1.00
LN0 NPI > 3.4	0.09	0.91	0.26	0.74
LN0 (one to three nodes)	0.44	0.56	0.73	0.27

**Deterministic sensitivity analysis**

The results of the DSAs for EPCLin are presented in *Table 49* (shaded cells reflect analyses that are unchanged from the EAG’s base case). The DSAs indicate the following:

- LN0 NPI ≤ 3.4 – the ICER for EPCLin versus current practice remains in excess of £91,000 per QALY gained across all scenarios.
- LN0 NPI > 3.4 – the ICER for EPCLin versus current practice remains in excess of £30,000 per QALY gained across almost all of the analyses. The exceptions are the scenarios in which (1) the UKBCG survey is used to inform the probability of receiving chemotherapy conditional on the EPCLin test result and (2) Cusumano *et al.*<sup>167</sup> is used to inform the probability of receiving chemotherapy conditional on the EPCLin test result.
- LN1–3 – the ICER for EPCLin versus current practice remains < £30,000 per QALY gained across all scenarios.

**MammaPrint versus current practice (Modified Adjuvant! Online)**

**Central estimates of cost-effectiveness: probabilistic**

Central estimates of cost-effectiveness for MammaPrint versus current practice (maOL) are presented in *Table 50*. Estimates are based on the probabilistic version of the EAG model. Within the overall MINDACT population, MammaPrint is expected to produce 0.01 additional QALYs at an additional cost of £1760 per woman tested compared with current practice; this corresponds to an ICER of £131,482 per QALY gained. Within the maOL high-risk subgroup, MammaPrint is expected to produce 0.04 fewer QALYs at an additional cost of £1413; within this subgroup, MammaPrint is expected to be dominated by current practice. Within the maOL low-risk subgroup, MammaPrint is expected to generate an additional 0.01 QALYs at an

TABLE 49 Deterministic sensitivity analyses: EPclin vs. current practice

Scenario	Subgroup								
	LN0 NPI ≤ 3.4			LN0 NPI > 3.4			LN1–3		
	Incremental QALYs	Incremental costs	ICER	Incremental QALYs	Incremental costs	ICER	Incremental QALYs	Incremental costs	ICER
Base case (deterministic)	0.01	£1685.68	£141,848	0.03	£1400.62	£46,482	0.06	£1184.94	£21,489
Post-test P(chemotherapy) (UKBCG survey)	0.01	£1470.85	£101,514	0.06	£1630.80	£25,250	0.12	£1632.35	£13,132
Chemotherapy disutility doubled	0.01	£1685.68	£181,242	0.03	£1400.62	£46,938	0.06	£1184.94	£21,140
Chemotherapy disutility halved	0.01	£1685.68	£127,943	0.03	£1400.62	£46,257	0.05	£1184.94	£21,667
Risk classification and DMFS (Dubsky <i>et al.</i> <sup>119</sup> LN+ subgroup)	0.01	£1685.68	£141,848	0.03	£1400.62	£46,482	0.05	£1179.22	£21,450
Post-test P(chemotherapy) (Penault-Llorca <i>et al.</i> <sup>56</sup> LN0 subgroup)	0.02	£1515.12	£91,800	0.04	£1425.80	£33,212	0.06	£1184.94	£21,489
Post-test P(chemotherapy) (Cusumano <i>et al.</i> <sup>167</sup> )	0.02	£1673.61	£109,964	0.06	£1532.67	£26,689	0.14	£1668.00	£12,205
10% lower cost per test owing to increased efficiency (local NHS testing)	0.01	£1536	£129,225	0.03	£1251	£41,504	0.06	£1035	£18,768
Start age based on TransATAC <sup>38,46</sup> (64 years)	0.01	£1687.17	£194,520	0.02	£1403.45	£60,061	0.04	£1190.15	£27,705
Farkkila <i>et al.</i> <sup>204</sup> utilities (RFS = 0.818, DM = 0.746)	0.01	£1685.68	£150,858	0.03	£1400.62	£48,314	0.05	£1184.94	£22,275
Chemotherapy RR = 0.70	0.02	£1664.55	£99,445	0.04	£1368.43	£36,317	0.07	£1130.67	£16,663
Chemotherapy RR = 0.80	0.01	£1699.55	£195,508	0.03	£1421.74	£56,485	0.05	£1220.54	£26,089
No risk tapering	0.02	£1638.80	£94,376	0.03	£1380.99	£41,242	0.06	£1146.32	£18,707
Distant metastases death rate doubled	0.01	£1724.04	£116,644	0.03	£1458.96	£42,242	0.06	£1283.29	£20,510
Distant metastases death rate halved	0.01	£1624.61	£223,409	0.02	£1307.57	£56,592	0.04	£1028.09	£23,745
AML removed	0.02	£1681.60	£99,734	0.03	£1402.34	£46,797	0.05	£1190.90	£22,954

continued

**TABLE 49** Deterministic sensitivity analyses: EPclin vs. current practice (*continued*)

Scenario	Subgroup								
	LN0 NPI ≤ 3.4			LN0 NPI > 3.4			LN1-3		
	Incremental QALYs	Incremental costs	ICER	Incremental QALYs	Incremental costs	ICER	Incremental QALYs	Incremental costs	ICER
Chemotherapy cost doubled	0.01	£1899.47	£159,838	0.03	£1424.85	£47,286	0.06	£1109.61	£20,122
Chemotherapy cost halved	0.01	£1578.79	£132,853	0.03	£1388.51	£46,080	0.06	£1222.61	£22,172
Endocrine therapy costs doubled	0.01	£1685.77	£141,855	0.03	£1400.80	£46,488	0.06	£1185.25	£21,494
Endocrine therapy costs halved	0.01	£1685.64	£141,844	0.03	£1400.53	£46,479	0.06	£1184.79	£21,486
Local and distant recurrence costs doubled	0.01	£1599.30	£134,579	0.03	£1269.24	£42,122	0.06	£963.46	£17,472
Local and distant recurrence costs halved	0.01	£1728.87	£145,482	0.03	£1466.31	£48,662	0.06	£1295.69	£23,497

DM, distant metastasis; P(chemotherapy), probability of receiving chemotherapy; RFS, recurrence-free survival.

**Note**

Shaded cells reflect analyses that are unchanged from the EAG's base case.

**TABLE 50** Central estimates of cost-effectiveness: MammaPrint vs. current practice (mAOL) – probabilistic model

Option	QALYs	Costs	Incremental QALYs	Incremental costs	ICER (per QALY gained)
<b>MINDACT ITT population</b>					
MammaPrint	13.51	£9151	0.01	£1760	£131,482
No test	13.49	£7391	–	–	–
<b>MINDACT mAOL high-risk subgroup</b>					
MammaPrint	12.86	£12,727	–0.04	£1413	Dominated
No test	12.90	£11,313	–	–	–
<b>MINDACT mAOL low-risk subgroup</b>					
MammaPrint	13.70	£7777	0.01	£2410	£414,202
No test	13.69	£5366	–	–	–

additional cost of £2410; this corresponds to an expected ICER of £414,202 per QALY gained. The PSA indicates that within the overall MINDACT population and both subgroups, the probability that MammaPrint produces more net benefit than current practice at WTP thresholds of £20,000 and £30,000 per QALY gained is approximately zero (Table 51).

### Deterministic sensitivity analysis

The results of the DSAs for MammaPrint are presented in Table 52 (shaded cells reflect analyses that are unchanged from the EAG's base case). The DSAs indicate the following:

- Within the overall MINDACT population, the ICER for MammaPrint versus current practice is estimated to be > £76,000 per QALY gained across all scenarios.
- Within the mAOL high-risk subgroup, MammaPrint is dominated by current practice across almost all scenarios. The most favourable ICER relates to the scenario in which the probability of receiving chemotherapy under current practice is halved.
- Within the mAOL low-risk subgroup, the ICER for MammaPrint versus current practice is > £161,000 per QALY gained across all analyses.

**TABLE 51** Probability of optimality: MammaPrint vs. current practice (mAOL)

Subgroup	Probability ( $\lambda = £20,000$ per QALY gained)		Probability ( $\lambda = £30,000$ per QALY gained)	
	MammaPrint	Current practice	MammaPrint	Current practice
MINDACT overall population	0.00	1.00	0.00	1.00
mAOL high-risk subgroup	0.00	1.00	0.00	1.00
mAOL low-risk subgroup	0.00	1.00	0.00	1.00

**TABLE 52** Deterministic sensitivity analyses: MammaPrint vs. current practice (mAOL)

Scenario	Subgroup								
	MINDACT ITT population			MINDACT mAOL high-risk subgroup			MINDACT mAOL low-risk subgroup		
	Incremental QALYs	Incremental costs	ICER	Incremental QALYs	Incremental costs	ICER	Incremental QALYs	Incremental costs	ICER
Base case (deterministic)	0.01	£1756.58	£134,059	-0.04	£1380.11	Dominated	0.01	£2415.05	£399,182
Risk classification and DMFS probabilities (van 't Veer <i>et al.</i> <sup>91</sup> )	0.01	£1609.52	£169,183	-0.04	£1380.11	Dominated	0.01	£2415.05	£399,182
ER+, HER2-, LNO subgroup	0.01	£1756.58	£134,059	-0.04	£1400.94	Dominated	0.01	£2415.05	£399,182
Post-test P(chemotherapy) (Penault-Llorca <i>et al.</i> <sup>56</sup> LNO subgroup)	0.02	£1724.59	£97,939	-0.03	£1386.99	Dominated	0.01	£2291.88	£257,484
Post-test P(chemotherapy) (Cusumano <i>et al.</i> <sup>167</sup> )	0.02	£1874.42	£91,453	-0.01	£1492.18	Dominated	0.01	£2454.55	£336,904
Post-test P(chemotherapy) (UKBCG)	0.01	£1610	£130,970	-0.01	£1601	Dominated	-0.01	£3421	Dominated
MammaPrint low-risk patients receive no chemotherapy; MammaPrint high-risk patients all receive chemotherapy	0.02	£1846.54	£76,201	0.00	£1497.09	£375,444	0.01	£2350.50	£242,895
Baseline chemotherapy probabilities halved	0.03	£2512.88	£96,782	0.07	£2243.31	£32,800	0.00	£2704.26	£903,528
Chemotherapy disutility doubled	0.02	£1756.58	£93,877	-0.03	£1380.11	Dominated	0.00	£2415.05	£503,351
Chemotherapy disutility halved	0.01	£1756.58	£170,560	-0.05	£1380.11	Dominated	0.01	£2415.05	£361,750
Start age based on TransATAC <sup>38,46</sup> (64 years)	0.01	£1757.57	£158,110	-0.03	£1374.22	Dominated	0.00	£2415.84	£547,979
Farkkila <i>et al.</i> <sup>204</sup> utilities (RFS = 0.818, DM = 0.746)	0.01	£1756.58	£133,215	-0.04	£1380.11	Dominated	0.01	£2415.05	£423,893
Chemotherapy RR = 0.70	0.01	£1762.13	£148,424	-0.06	£1431.22	Dominated	0.01	£2377.25	£161,338
Chemotherapy RR = 0.80	0.01	£1753.86	£127,971	-0.03	£1296.55	Dominated	0.01	£2403.58	£276,670
No risk tapering	0.01	£1784.24	£173,280	-0.07	£1591.64	Dominated	0.01	£2391.23	£270,639

Scenario	Subgroup								
	MINDACT ITT population			MINDACT mAOL high-risk subgroup			MINDACT mAOL low-risk subgroup		
	Incremental QALYs	Incremental costs	ICER	Incremental QALYs	Incremental costs	ICER	Incremental QALYs	Incremental costs	ICER
Distant metastases death rate doubled	0.01	£1747.73	£140,551	-0.06	£1218.99	Dominated	0.01	£2434.08	£325,055
Distant metastases death rate halved	0.01	£1770.62	£125,010	-0.03	£1636.40	Dominated	0.00	£2384.61	£636,029
AML removed	0.00	£1768.44	£1,353,592	-0.07	£1401.41	Dominated	0.01	£2413.62	£291,353
Chemotherapy cost doubled	0.01	£1292.39	£98,632	-0.04	£351.31	Dominated	0.01	£2518.68	£416,311
Chemotherapy cost halved	0.01	£1988.67	£151,772	-0.04	£1894.51	Dominated	0.01	£2363.24	£390,617
Endocrine therapy costs doubled	0.01	£1756.59	£134,060	-0.04	£1379.77	Dominated	0.01	£2415.09	£399,189
Endocrine therapy costs halved	0.01	£1756.57	£134,058	-0.04	£1380.28	Dominated	0.01	£2415.03	£399,178
Local and distant recurrence costs doubled	0.01	£1776.51	£135,580	-0.04	£1743.07	Dominated	0.01	£2372.26	£392,109
Local and distant recurrence costs halved	0.01	£1746.61	£133,298	-0.04	£1198.63	Dominated	0.01	£2436.45	£402,719

DM, distant metastasis; P(chemotherapy), probability of receiving chemotherapy; RFS, recurrence-free survival.

**Note**  
Shaded cells reflect analyses that are unchanged from the EAG's base case.

### **Comparison between the Genomic Health model, the current External Assessment Group model and the previous External Assessment Group model (lymph node negative, clinical intermediate-risk subgroup)**

There are notable differences between the cost-effectiveness estimates for onco $type$  DX versus current practice generated using the current EAG model and those produced using the Genomic Health model<sup>62</sup> (see *Appendix 7*) and the earlier EAG model reported by Ward *et al.*:<sup>1</sup>

- The current EAG model indicates that within the ER+ LNO NPI > 3.4 subgroup, onco $type$  DX is expected to be dominated by current practice. This finding sharply contrasts with the findings of the Genomic Health model and the previous EAG model.
- The Genomic Health model<sup>62</sup> produces a base-case ICER of (confidential information has been removed) per QALY gained, assuming that the test is used for women with ER+, LNO early-stage breast cancer who are deemed to be at clinical intermediate risk.
- The previous EAG model (Ward *et al.*<sup>1</sup>) produced a base-case ICER for onco $type$  DX versus current practice of £22,572 per QALY gained, assuming that the test is given to women with ER+, LNO early-stage breast cancer with NPI > 3.4 (deemed to be at clinical intermediate risk).

In order to understand the differences between these results, it is important to consider the differences between the key parameters and structural assumptions between the three models (*Table 53*):

- The general modelling approach is very similar between the three models, although the Ward *et al.*<sup>1</sup> model defined test risk classification in accordance with both onco $type$  DX Breast Recurrence Score and IHC4, rather than onco $type$  DX Breast Recurrence Score only.
- Within the original and current EAG models, data on risk reclassification (the proportion of patients with a low, intermediate and high recurrence score) were taken from analyses of the TransATAC trial<sup>46</sup> (albeit using different data sets). Conversely, the Genomic Health model derives these proportions from the NHS England Access Scheme Database.<sup>183</sup>
- Data on the risk of distant recurrence in the absence of chemotherapy were taken from the ATAC trial in all three models.<sup>198</sup> The updated EAG model uses newer data from the ATAC trial.<sup>46</sup>
- The proportions of women who are assumed to receive chemotherapy conditional on the onco $type$  DX risk score were taken from the NHS England Access Scheme Database<sup>183</sup> in both the updated EAG model and the Genomic Health model. Ward *et al.*<sup>1</sup> used unpublished data (Holt *et al.*<sup>141</sup>) to estimate the probability of receiving chemotherapy conditional on onco $type$  DX Breast Recurrence Score.
- The proportion of patients receiving chemotherapy in the standard care arm was taken from the NHS England Access Scheme Database<sup>183</sup> in both the updated EAG model and the Genomic Health model. Conversely, Ward *et al.*<sup>1</sup> derived estimates of these proportions from English cancer registry data sets.
- Within both the current and earlier EAG models, the benefit of chemotherapy was assumed to be constant across all onco $type$  DX Breast Recurrence Score classifications (non-predictive); the RR of distant recurrence was taken from EBCTCG meta-analyses. The current EAG model uses a different mathematical approach to apply this RR, which ensures that modelled treatment effect at 10 years is maintained within the Markov trace.
- The Genomic Health model assumes a predictive benefit and uses different treatment effects across the low, intermediate and high recurrence score classifications, based on Paik *et al.*<sup>50</sup> These differential effects are applied only to the onco $type$  DX testing group; a constant treatment effect is applied in the current practice group.
- The current and earlier EAG models both apply a HRQoL decrement associated with short-term chemotherapy-related AEs in the first model cycle. In contrast, the Genomic Health model applies a decrement during every model cycle; the implicit assumption is that patients who receive adjuvant chemotherapy remain less well, relative to those do not receive adjuvant chemotherapy, for the remainder of their lives.

TABLE 53 Summary of structural assumptions and evidence sources

Assumption/evidence source	Current EAG model	Genomic Health model <sup>62</sup>	Original EAG model (Ward <i>et al.</i> <sup>1</sup> )
Approach	Risk classification based on <i>onco</i> type DX RS	Risk classification based on <i>onco</i> type DX RS	Risk classification based on <i>onco</i> type DX RS and IHC4
Data on risk classification	TransATAC <sup>46</sup>	NHS England Access Scheme Database <sup>183</sup>	TransATAC <sup>46</sup>
Data on ROR	TransATAC <sup>46</sup> (updated)	TransATAC <sup>46</sup>	TransATAC <sup>46</sup>
Proportion of people receiving chemotherapy in the <i>onco</i> type DX arm	NHS England Access Scheme Database <sup>183</sup>	NHS England Access Scheme Database <sup>183</sup>	Holt <i>et al.</i> <sup>141</sup>
Proportion of people receiving chemotherapy in the standard care arm	NHS England Access Scheme Database <sup>183</sup>	NHS England Access Scheme Database <sup>183</sup>	Registry data
Benefit of adjuvant chemotherapy	No predictive effect (based on EBCTCG meta-analysis)	Predictive effect only in the <i>onco</i> type DX group. No predictive effect assumed in people with same risk score in current practice group	No predictive effect (based on EBCTCG meta-analysis)
HRQoL decrement associated with chemotherapy	Applied to the first cycle only	Applied to all model cycles over patients' remaining lifetimes	Applied to the first cycle only

RS, recurrence score.

As described in *Appendix 7*, the EAG identified several errors within the Genomic Health model. Three key errors are corrected here:

1. The application of risk reclassification in the model. Although Genomic Health use data from the NHS England Access Scheme Database for the risk reclassification, this is applied incorrectly in the model. This can be seen by examining the proportion of women receiving chemotherapy predicted by the model. The NHS England Access Scheme data were provided as AiC and cannot be reported here.<sup>62</sup>
2. The application of the HRQoL decrement associated with chemotherapy-related AEs. The Genomic Health dossier<sup>62</sup> stated that the utilities in their model were the same as those used by Ward *et al.* (2013)<sup>1</sup> (page 159), and Table 6-4 (page 159) of the dossier states that the disutility associated with chemotherapy is  $-0.038$ . However, the Genomic Health model applies this decrement for women receiving chemotherapy during every model cycle, including for decades after the adjuvant treatment has been discontinued. This overestimates the health losses associated with chemotherapy and is therefore favourable to *onco*type DX, as the test is estimated to reduce the proportion of women receiving chemotherapy.
3. Predictive chemotherapy benefit. The Genomic Health model assumes that women with a low, intermediate and high *onco*type DX Breast Recurrence Score experience different benefits of chemotherapy in the modelled *onco*type DX group compared with the same patients across these recurrence score classifications in the modelled current practice group. Irrespective of whether *onco*type DX is predictive of chemotherapy benefit, the modelling approach adopted by the company is illogical, as the benefits of chemotherapy for women within these recurrence score classifications will be identical irrespective of whether the test is used to classify that level of risk or not (they are exactly the same patients).

In order to understand the differences between the results of the three models, the errors identified above were corrected by the EAG. In addition, the Genomic Health model was modified to assume a prognostic benefit only, thereby making it consistent with the current EAG base-case model. The earlier EAG model (Ward *et al.*<sup>1</sup>) was also modified to include the chemotherapy probabilities (with and without the test) from

the NHS England Access Scheme Database. Although there are other differences between the models, these are more difficult to align across the models and/or are expected to have only a negligible impact on results. The results of the current EAG model, the amended Ward *et al.*<sup>1</sup> model and the corrected Genomic Health model are presented in *Table 54*.

In the scenario in which all three models use pre- and post-test chemotherapy probabilities from the NHS England Access Scheme Database and no predictive benefit is assumed, all three models produce the same economic conclusion: *oncotype DX* is dominated by current practice. When a predictive effect is incorporated into these versions of the models, these three models consistently suggest that *oncotype DX* has an ICER that is < £7000 per QALY gained.

## Discussion

The EAG undertook a systematic review of existing economic evaluations of tumour profiling tests to guide treatment decisions in people with early-stage breast cancer (see *Appendix 6*). Only those studies that were published since the previous appraisal of tumour profiling tests (NICE DG10<sup>20</sup>) were included in the review. The review suggests a high level of consistency in terms of the general modelling approach and structure: the majority of published models adopted a decision tree–Markov approach based on test risk classification and DMFS outcomes conditional on test risk classification probabilities. None of the published analyses included all relevant tumour profiling tests listed in the final NICE scope.

Two manufacturers provided economic evidence to inform the appraisal (Agendia<sup>94</sup> and Genomic Health<sup>62</sup>) (see *Appendix 7*). The models developed to inform these two analyses were made available to the EAG for scrutiny. In addition, the chief investigator of the EndoPredict UK decision impact study provided a draft cost-effectiveness paper that compares EPclin with AOL.<sup>182</sup> The model supporting this analysis was not made available to the EAG.

Agenda submitted a model, which was critiqued by the EAG as part of the assessment process, but it cannot be reported here as Agendia withdrew permission to reproduce the model.

Genomic Health provided a model that compares *oncotype DX* with current practice in patients with LNO early-stage breast cancer. The EAG notes that the model includes a number of errors. Based on the uncorrected model, the Genomic Health submission presents a base-case ICER for *oncotype DX* versus current practice of (confidential information has been removed) per QALY gained. Three errors were corrected by the EAG [see *Comparison between the Genomic Health model, the current External Assessment Group model and the previous External Assessment Group model (lymph node-negative, clinical intermediate-risk subgroup)*]; these relate to (1) the incorrect application of risk classifications, (2) the application of health losses associated with short-term chemotherapy-related AEs during every model cycle and (3) the inconsistent handling of predictive benefits of chemotherapy between the test and no-test groups. The EAG's corrected version of the model suggests that under the assumption of no predictive benefit of chemotherapy, *oncotype DX* is dominated by current practice. When the test is assumed to be predictive of chemotherapy benefit, the ICER for *oncotype DX* versus current practice is estimated to be (confidential information has been removed) per QALY gained. The EAG notes that other errors may remain within the company's model.

The draft cost-effectiveness paper assessing EPclin versus AOL suggests that the expected ICER for EPclin versus AOL is £26,836 per QALY gained. The EAG has some concerns regarding this analysis, in particular the use of separate evidence sources to estimate test risk classification probabilities and DMFS probabilities conditional on test risk classification.

**TABLE 54** Comparison of ICERs generated using the current EAG model, the previous EAG model and the Genomic Health model (LN0 NPI > 3.4 subgroup)

Model	QALYs		Costs		Incremental QALYs	Incremental costs	ICER
	Oncotype DX	No test	Oncotype DX	No test			
<b>Assuming no predictive effect</b>							
Current EAG model (no predictive effect)	12.68	12.70	£11,249	£10,380	-0.02	£869	Dominated
Uncorrected Genomic Health model <sup>62</sup> (with predictive effect)	10.50	10.43	Confidential information has been removed	Confidential information has been removed	0.07	Confidential information has been removed	Confidential information has been removed
Corrected Genomic Health model (no predictive effect)	10.59	10.62	Confidential information has been removed	Confidential information has been removed	-0.03	Confidential information has been removed	Confidential information has been removed
Ward <i>et al.</i> <sup>1</sup> model (no predictive effect)	12.85	12.80	£10,172	£8897	0.06	£1275	£22,572
Ward <i>et al.</i> <sup>1</sup> model, including NHS England Access Scheme Database for proportion of people who receive chemotherapy (no predictive effect)	12.83	12.83	£9861	£9253	-0.00	£608	Dominated
<b>Assuming predictive effect</b>							
Current EAG model (predictive effect)	12.87	12.60	£10,457	£10,822	0.27	-£364	Dominating
Uncorrected Genomic Health model <sup>62</sup> (predictive effect)	10.50	10.43	Confidential information has been removed	Confidential information has been removed	0.07	Confidential information has been removed	Confidential information has been removed
Corrected Genomic Health model (predictive effect)	10.74	10.69	Confidential information has been removed	Confidential information has been removed	0.05	Confidential information has been removed	Confidential information has been removed
Ward <i>et al.</i> <sup>1</sup> model (predictive effect)	13.06	12.83	£9681	£8816	0.23	£865	£3720
Ward <i>et al.</i> <sup>1</sup> model, including NHS England Access Scheme Database for proportion of people who receive chemotherapy (including predictive effect)	13.02	12.91	£9412	£9078	0.11	£334	£2917

The EAG developed a de novo health economic model to assess the cost-effectiveness of *oncotype* DX, MammaPrint, Prosigna, EPclin and IHC4+C, each versus current practice. The health economic analysis was undertaken from the perspective of the NHS and PSS and was largely based on the model developed to inform NICE DG10.<sup>1</sup> The EAG model adopts a hybrid decision tree–Markov structure. The model parameters were informed by a number of sources including a bespoke analysis of the TransATAC trial,<sup>46</sup> the MINDACT trial,<sup>98</sup> a bespoke analysis of the NCRAS data set,<sup>184</sup> a bespoke survey disseminated by the UKBCG, the NHS England Access Scheme Database,<sup>183</sup> standard costing sources and other literature. The EAG’s base-case model suggests the following results.

- *Oncotype* DX – within the LN0 NPI  $\leq 3.4$  subgroup, the ICER for *oncotype* DX versus current practice is expected to be £122,725 per QALY gained (£34,245 per QALY gained assuming a predictive benefit). Within the LN0 NPI  $> 3.4$  and LN1–3 subgroups, *oncotype* DX is expected to be dominated by current practice (conversely, *oncotype* DX dominates current practice if a predictive benefit is assumed). The results generated using the EAG model are primarily driven by the modelled reduction in the use of adjuvant chemotherapy using the *oncotype* DX test.
- IHC4+C – within the LN0 NPI  $\leq 3.4$  subgroup, the ICER for IHC4+C versus current practice is expected to be £2654 per QALY gained. Within the LN0 NPI  $> 3.4$  and LN1–3 subgroups, IHC4+C is expected to dominate current practice.
- Prosigna – within the LN0 NPI  $\leq 3.4$  subgroup, the ICER for Prosigna versus current practice is expected to be £91,028 per QALY gained. Within the LN0 NPI  $> 3.4$  and LN1–3 subgroups, the ICERs for Prosigna versus current practice are £26,058 and £28,731 per QALY gained, respectively.
- EPclin – within the LN0 NPI  $\leq 3.4$  subgroup, the ICER for EPclin versus current practice is expected to be £147,419 per QALY gained. Within the LN0 NPI  $> 3.4$  subgroup, the ICER for EPclin versus current practice is expected to be £46,788 per QALY gained. Within the LN1–3 subgroup, the ICER for EPclin versus current practice is expected to be £21,458 per QALY gained.
- MammaPrint – within the overall MINDACT population, the ICER for MammaPrint versus current practice is expected to be £131,482 per QALY gained. Within the mAOL high-risk subgroup, MammaPrint is expected to be dominated by current practice. Within the mAOL low-risk subgroup, the ICER for MammaPrint versus current practice is expected to be £414,202 per QALY gained.

The EAG model is subject to the following strengths:

- The model structure is consistent with the general approach used in a number of previous economic analyses of tumour profiling tests for early-stage breast cancer (see *Appendix 6, Tables 69 and 70*).
- For all tests, test risk classification probabilities and DMFS probabilities are derived from the same source – this maintains correlation between these parameters and avoids the potential for spectrum bias to produce spurious results.
- Within the LN0 intermediate-risk subgroup (NPI  $> 3.4$ , analysis of three-level tests), the probability of receiving chemotherapy with and without the test is based on the same source – the NHS England Access Scheme Database.<sup>183</sup> The EAG takes the view that this source is likely to best reflect how the three-level tumour profiling tests would be used in clinical practice in England. However, this evidence source relates only to the clinical intermediate-risk group; the UK-specific evidence surrounding decision impact within the LN0 NPI  $\leq 3.4$  and LN+ subgroups is considerably weaker.
- When based on the same test risk classification probabilities, recurrence rates and the same estimates of pre- and post-test chemotherapy use, the EAG model produces similar results to the previous model reported by Ward *et al.*<sup>1</sup> and the Genomic Health model.<sup>62</sup>
- A large number of scenarios have been considered to explore the impact of alternative evidence choices and assumptions on the cost-effectiveness of the alternative tests.

The EAG model is also subject to a number of limitations and uncertainties:

- Test risk classification probabilities and DMFS probabilities for *oncotype* DX, Prosigna, IHC4+C and EPclin are based on a postmenopausal population only (TransATAC). It is expected that the tumour profiling tests may also be used in premenopausal women.

- The subgroups employed within the analysis are defined in accordance with NPI. In practice, other tools may be used to define risk (e.g. Predict). The EAG explored the possibility of framing the analyses around Predict; however, this was not possible as Predict scores were not available within either the TransATAC data set or the NCRAS data set, nor was an analysis presented by Predict within the publication of the MINDACT trial.<sup>98</sup> It may be possible to calculate Predict scores within these data sets in the future; however this would require access to the individual patient-level data.
- The analysis of MammaPrint using the MINDACT trial compares the test only against mAOL and may therefore not reflect current practice in England. This issue is particularly relevant to determining the baseline level of chemotherapy use for the current practice group within this population.
- Within the current practice group of the EAG model, the probability of receiving chemotherapy is assumed to be the same irrespective of test risk score. This is unlikely to be realistic, as those with higher test risk scores may already be more likely to receive adjuvant chemotherapy, and those with lower test risk scores may already be less likely to receive adjuvant chemotherapy. It was possible to explore this assumption for the evaluation of *oncotype* DX within the sensitivity analyses (and the conclusions were unchanged); however, there were insufficient data available to undertake similar analyses for the other four tests.
- The TransATAC trial was the derivation study for IHC4+C. This means that there is potential for the overestimation of prognostic performance; this leads to additional uncertainty around the likely cost-effectiveness profile of this test.
- The MINDACT trial used to inform the analyses of MammaPrint is limited as this study does not provide information regarding predictive benefit. In addition, the follow-up period for this study was limited to a duration of 5 years.
- Across all analyses, it is clear that the model results are dependent on assumptions about pre- and post-test chemotherapy use. This aspect of the evidence base is subject to considerable uncertainty. In particular, there is only one UK-based decision impact study relating to a two-level tumour profiling test (Bloomfield *et al.*<sup>159</sup>); the characteristics of patients enrolled into this study, and their relevance to the modelled subgroups, are unclear. As shown in the DSAs, the use of alternative European studies<sup>162,167</sup> and the UKBCG survey appear to lead to generally more favourable cost-effectiveness estimates for EPclin and MammaPrint. In addition, the use of the Lancaster *et al.*<sup>145</sup> study to estimate chemotherapy use in the LN+ population may be biased as this study included a preselected population for whom chemotherapy had already been recommended.
- As NanoString Technologies does not offer a centralised testing service for Prosigna, the cost per test will depend on the efficiency of local testing centres and the number of tests undertaken within each centre. This may affect the cost-effectiveness estimates presented here.
- The model does not include CHF as a long-term AE associated with adjuvant chemotherapy; this was excluded from the model owing to a lack of evidence on the joint survival impact of CHF and metastatic breast cancer. Although CHF is a more common event than AML, the development of cancer is likely to have more serious consequences and is expected to be associated with a greater impact on health-care resources.
- There is uncertainty surrounding whether or not *oncotype* DX is predictive of chemotherapy benefit; based on the current EAG model, the inclusion of this potential test characteristic has a marked impact on the conclusions drawn from the analysis. Although the ongoing TAILORx study may generate additional evidence to inform this, the cut-off points used within this trial differ from those employed within the TransATAC analysis.
- Overall, there remains uncertainty regarding the cost-effectiveness of all tests. It is noteworthy that the inclusion of additional data collected through the NHS England Access Scheme Database has a significant impact on the conclusions drawn from the *oncotype* DX analysis within NICE DG10<sup>20</sup> (moving from an ICER of £22,572 per QALY gained to a situation in which *oncotype* DX is dominated in the LN0 NPI > 3.4 subgroup). The EAG considers that additional UK-based data collection relating to pre- and post-test chemotherapy use for EPclin, IHC4+C, Prosigna and MammaPrint may be important in reducing existing uncertainty surrounding the cost-effectiveness of these tests.



# Chapter 4 Discussion and conclusions

## Statement of principal findings

### *Clinical effectiveness: principal findings*

The review included 153 studies across all five tests and across all outcomes listed in the NICE scope.

Among studies of LN0 patients receiving endocrine monotherapy, percentages categorised as high risk ranged from 9% to 33% across all five tests. In LN+ patients, three tests (Prosigna/ROR-PT, EPclin and IHC4+C) categorised far more (38% to 76%) LN+ patients than LN0 patients as being at high risk among studies of endocrine monotherapy, whereas *oncotype* DX categorised a similar number as high risk in LN0 and LN+ groups. However, *oncotype* DX categorised more patients in the LN+ group as being at low risk than other tests (57% for *oncotype* DX vs. 4–28% for other tests), but with worse 10-year DRFS/DRFI outcomes (82% for *oncotype* DX vs. 95–100% for other tests).

In terms of prognostic performance, all tests had statistically significant prognostic power in unadjusted analyses in LN0 and LN+ populations. However, RSPC was only validated in LN0 patients, and unadjusted analyses using clinical cut-off points were not reported in the validation sets for IHC4 or IHC4+C. All tests provided additional prognostic information over most commonly used clinicopathological factors and over CTS and NPI in LN0 patients. Results were more varied in LN+ patients.

There was some evidence of differential chemotherapy benefit between risk groups for *oncotype* DX, as shown by significant interaction tests between risk group and chemotherapy treatment in unadjusted analyses, but interaction tests sometimes became non-significant when clinicopathological factors were adjusted for and key LN0 data came from the derivation cohort (NSABP B-20) for *oncotype* DX, putting it at high risk of bias. *Oncotype* DX RSPC (*oncotype* DX plus age, tumour size and grade) was prognostic but not statistically significantly predictive for chemotherapy benefit, indicating that the incorporation of clinicopathological factors (formally or informally in a clinical setting) in *oncotype* DX may reduce prediction of chemotherapy benefit; this study also used NSABP B-20 and is at risk of bias as a consequence. Considering the limitations of the available data, the EAG concludes that there remains uncertainty surrounding whether or not *oncotype* DX is associated with a predictive benefit of chemotherapy (i.e. a difference in relative effect by genomic risk group) and, if so, that there is uncertainty in the likely magnitude of this predictive effect in clinical practice.

Evidence relating to the ability of MammaPrint to predict benefit from chemotherapy was extremely limited. Although the effect of chemotherapy was significant in high-risk groups and not in low-risk groups, interaction tests between risk groups and chemotherapy treatment were not significant, suggesting that there was no statistically significant difference in the effect of chemotherapy between risk groups.

For *oncotype* DX and MammaPrint, evidence from observational, non-comparative studies assessing the impact of the test used prospectively in clinical practice suggested that recurrence/survival outcomes in low-risk groups were acceptable even with low rates of chemotherapy. There was no similar evidence relating to the other tests.

The MINDACT RCT for MammaPrint<sup>98</sup> was the only RCT to have reported in full. It reported that for patients who were high mAOL, low MammaPrint risk, chemotherapy gave a non-significant absolute benefit of 1.5% in 5-year DMFS ( $p = 0.267$ ). This met the primary objective in that the lower bound of the 95% CI for 5-year DMFS in the no-chemotherapy group was  $\geq 92\%$ . This finding was interpreted by the authors as implying that patients who were high clinical risk but low MammaPrint risk could potentially avoid chemotherapy. In patients who were low mAOL risk, high MammaPrint risk, chemotherapy gave an

absolute benefit of 0.8%. This could be interpreted to mean that MammaPrint would not be a useful test in mAOL-low-risk patients, as it would not alter treatment decisions.

Decision impact studies from the UK and Europe reported that the percentage of patients with any change in chemotherapy recommendation or decision pre/post test ranged from 27% to 49% across UK studies (included *oncoType* DX, EndoPredict and IHC4+C) and from 5% to 70% across European studies (included all tests except IHC4). The net change in the percentage of patients with a chemotherapy recommendation or decision pre/post test ranged from an increase of 1% to a decrease of 23% among UK studies and from a decrease of 0% to a decrease of 64% across European studies.

Concordance between tests was not fully reviewed, but one UK study (OPTIMA Prelim<sup>30</sup>), which compared *oncoType* DX, MammaPrint, Prosigna and IHC4, concluded that although tests assigned similar proportions of patients to low/intermediate- and high-risk categories, test results for an individual patient could differ markedly depending on which test was used.

Data relating to anxiety and HRQoL were limited as most studies did not include a comparator, instead adopting a pre–post test design. Anxiety generally reduced post test, but it is unclear to what extent this would happen after a definitive treatment decision made in accordance with clinical factors. HRQoL improved in some analyses.

Microarray studies support conclusions from studies using the commercial versions of the assays in suggesting that *oncoType* DX, MammaPrint and EndoPredict can discriminate between high- and low-risk patients regardless of LN status (there were no relevant microarray studies for Prosigna or IHC4).

### **Cost-effectiveness: principal findings**

The EAG developed a de novo health economic model to assess the cost-effectiveness of *oncoType* DX, MammaPrint, Prosigna, EPclin and IHC4+C, each versus current practice. The health economic analysis was undertaken from the perspective of the NHS and PSS and was largely based on the model developed to inform NICE DG10.<sup>20</sup> The EAG model adopts a hybrid decision tree–Markov structure. The model parameters were informed by a number of sources including a bespoke analysis of the TransATAC trial, the MINDACT trial, a bespoke analysis of the NCRAS data set, a bespoke survey disseminated by the UKBCG, the NHS England Access Scheme Database, standard costing sources and other literature. The EAG's base-case model suggests the following results:

- *OncoType* DX – within the LN0 NPI  $\leq 3.4$  subgroup, the ICER for *oncoType* DX versus current practice is expected to be £122,725 per QALY gained (£34,245 per QALY gained assuming a predictive chemotherapy benefit). Within the LN0 NPI  $> 3.4$  and LN1–3 subgroups, *oncoType* DX is expected to be dominated by current practice (conversely, *oncoType* DX dominates current practice if a predictive chemotherapy benefit is assumed). The results generated using the EAG model are primarily driven by the modelled reduction in the use of adjuvant chemotherapy using the *oncoType* DX test.
- IHC4+C – within the LN0 NPI  $\leq 3.4$  subgroup, the ICER for IHC4+C versus current practice is expected to be £2654 per QALY gained. Within the LN0 NPI  $> 3.4$  and LN1–3 subgroups, IHC4+C is expected to dominate current practice.
- Prosigna – within the LN0 NPI  $\leq 3.4$  subgroup, the ICER for Prosigna versus current practice is expected to be £91,028 per QALY gained. Within the LN0 NPI  $> 3.4$  and LN1–3 subgroups, the ICERs for Prosigna versus current practice are £26,058 and £28,731 per QALY gained, respectively.
- EPclin – within the LN0 NPI  $\leq 3.4$  subgroup, the ICER for EPclin versus current practice is expected to be £147,419 per QALY gained. Within the LN0 NPI  $> 3.4$  subgroup, the ICER for EPclin versus current practice is expected to be £46,788 per QALY gained. Within the LN1–3 subgroup, the ICER for EPclin versus current practice is expected to be £21,458 per QALY gained.
- MammaPrint – within the overall MINDACT population, the ICER for MammaPrint versus current practice is expected to be £131,482 per QALY gained. Within the mAOL high-risk subgroup, MammaPrint is expected to be dominated by current practice. Within the mAOL low-risk subgroup, the ICER for MammaPrint versus current practice is expected to be £414,202 per QALY gained.

## Strengths and limitations of the assessment

### *Strengths and limitations in the clinical evidence base*

The clinical review benefited from a comprehensive search strategy and a high-quality, prospectively designed systematic review methodology.

The evidence base was large, but included only one RCT of a test being used in clinical practice versus usual clinical practice that had reported in full (MINDACT, for MammaPrint).<sup>98</sup> A number of reanalyses of RCTs, which are generally considered to be a high-quality source of data, were also included in the reviews of prognosis and prediction of chemotherapy benefit. However, nearly all studies excluded patients who did not have enough tissue sample (although this is unavoidable in retrospective analyses), which leaves the evidence base at potential risk of spectrum bias, as patients with smaller tumours (who may be systematically different from those with large tumours) will likely be under-represented.

Although, due to time constraints, we did not record every instance of industry funding for included studies, a large number of key studies were funded by industry, and the risk of bias from this should be borne in mind when interpreting the evidence base.

Many prognostic studies were observational in nature, and these are subject to confounding, whereby exclusion of patients who received chemotherapy is likely to introduce bias as these patients are likely to be systematically different in terms of known (and potentially unknown) prognostic variables. Equally, studies that included patients who received chemotherapy may underestimate prognostic effect and/or have more higher-risk patients included.

There were some key gaps in the literature for IHC4+C and RSPC. Notably, the IHC4+C algorithm has been validated only in one cohort (in an adjusted analysis), and RSPC has also been validated in only one cohort (in an unadjusted analysis, and for chemotherapy benefit). In both cases, the validation study was conducted as part of the derivation study. The IHC4/IHC4+C evidence base was also limited in that most of the data related to the IHC4 score alone, without the clinical score, and most studies used tertiles and quartiles to define low-, intermediate- and high-risk patients, which may not be useful in a clinical setting. In addition, there are known problems with conducting the analyses required for IHC4, and although a number of studies report methodologies that are largely compliant with the original methodology, it is unclear whether or not the absolute IHC4 values obtained would be similar across centres.

Much of the evidence base relates to unadjusted analyses, which do not assess the crucial question of whether or not a test has additional value over clinicopathological factors. When adjusted analyses were conducted, the clinicopathological variables included were not always consistent, and it is unclear if all important factors (including stratification factors from the original RCT studies, when applicable) were included in all analyses.

There were limited data relating to the ability of onco<sup>type</sup> DX and MammaPrint to predict benefit from chemotherapy, and some of the analyses conducted were also subject to criticisms relating to adjustment for all relevant variables. It may be difficult to conduct further such studies as there are few studies in which patients were randomised to chemotherapy versus no chemotherapy, and tissue samples may not be available.

Data relating to the ability of the test to affect patient outcomes (such as recurrence and survival) through the prospective use of the test to guide treatment decisions were also limited. Most studies were observational in nature, and the selection of patients on the basis of them having received a test may have introduced spectrum bias, and, for this reason, these studies may not match the decision problem. They also do not, by their nature, include a comparator arm, and it is difficult to draw any firm conclusions about the effect of the test in real clinical practice. Similarly, such studies that reported data relating to chemotherapy effects in different risk groups are subject to the same limitations in terms of spectrum bias,

but are also at risk of bias from confounding whereby patients who received chemotherapy are likely to be systematically different in terms of known (and potentially unknown) prognostic variables (e.g. age) and treatment effect modifiers from those who did not, which may have an impact on observed recurrence rates and estimates of chemotherapy benefit.

Retrospective observational studies (in which patients were treated in accordance with usual practice without the tests) reporting data relating to prognostic performance are also at risk of confounding in that chemotherapy rates per risk group may differ (and thus affect estimates of prognostic performance). Observational studies that excluded patients who received chemotherapy, in order to obtain a group of patients unaffected by treatment, are likely to be subject to spectrum bias, as patients who receive chemotherapy are likely to be systematically different from those who do not, and this may also affect estimates of prognostic performance. These problems were particularly relevant to the MammaPrint evidence base, in which most studies were observational in nature rather than reanalyses of RCTs. MammaPrint was also unusual, in that many of the included studies pooled multiple cohorts, and, for this reason, it was not possible to gauge the degree of double-counting of patients. The overall sample size was also low (total  $n = 1805$ ) compared with the evidence base for most other tests.

The evidence base relating to the impact of tests on treatment decisions (decision impact studies) was limited in that use of chemotherapy differs across countries and there were no UK studies for two tests (MammaPrint and Prosigna) and only one UK study for another two tests (EndoPredict and IHC4+C).

### ***Strengths and limitations relating to the health economic analysis***

The EAG model has a number of strengths; in particular:

- For all tests, risk classification and DMFS probabilities are derived from the same source (TransATAC or MINDACT).
- Within the LNO intermediate-risk subgroup (NPI > 3.4, analysis of three-level tests), the probability of receiving chemotherapy with and without the test is based on the NHS England Access Scheme Database – this is likely to best reflect how the three-level tumour profiling tests would be used in clinical practice in England.
- The model structure is consistent with that of other published models of tumour profiling tests – when similar data inputs are used, the EAG model produces similar results to the previous EAG model and the Genomic Health model.
- Extensive DSAs have been conducted to explore the impact of uncertainty on the model results.

However, the model is also subject to several limitations, most of which stem from uncertainties in the evidence base. The main limitations and uncertainties relating to the cost-effectiveness analysis are:

- With the exception of onco $type$  DX in the LNO NPI > 3.4 group (clinical intermediate risk), the evidence surrounding the pre- and post-test chemotherapy probabilities is subject to considerable uncertainty – this has the propensity to influence the conclusions regarding the cost-effectiveness of all tests.
- There is uncertainty regarding whether or not onco $type$  DX and MammaPrint are predictive of chemotherapy benefit – the inclusion of such effects are likely to strongly influence economic conclusions drawn from the analysis.
- The analysis of MammaPrint is based on a different data source than the other four tests.
- The TransATAC study used to estimate test risk classification and DMFS probabilities was the derivation study for IHC4 – for this reason, there is potential for the overestimation of prognostic performance for this test.

## Uncertainties

Because of time and data constraints, it was not possible to conduct a thorough analysis of how the baseline clinicopathological characteristics of patients (e.g. tumour grade, stage and age) affect prognostic performance.

The evidence relating to the impact on patient outcomes when the test is used in clinical practice remains largely unanswered, and is impeded by the long-term follow-up required, the large sample sizes required and ethical problems with withholding chemotherapy from clinically high-risk patients.

Evidence relating to key subgroups defined in the scope were largely lacking. Data relating specifically to micrometastases were rarely reported, there were no data at all in male-only subgroups or cohorts and data relating to people of different ethnicities were difficult to interpret due to differences in treatment practices in different countries. A more detailed consideration of the available evidence base may have allowed some observations to be drawn regarding premenopausal and postmenopausal patients, but time constraints prevented this.

The IHC4 test is known to have implementation issues in terms of conducting the test in other laboratories, especially local laboratories. The precise details are beyond the expertise of the EAG. It is uncertain if these could be overcome. Furthermore, it is somewhat unclear what cut-off values should be used for IHC4 and IHC4+C.

## Generalisability

The EAG notes that there may be issues relating to the generalisability of the evidence contained within this report. In particular, issues with spectrum bias (loss of patients with small tumours with insufficient tissue to test) were evident throughout the clinical evidence base. Furthermore, the classification of risk by NPI will not reflect current practice across all centres. In addition, the TransATAC study that was used to inform test risk classification and DMFS probabilities for oncotype DX, Prosigna, IHC4+C and EPclin relates only to a postmenopausal population only; it is expected that the tumour profile testing may also be used in premenopausal women.

## Implications for service provision

The per-test costs for Prosigna provided by NanoString Technologies (used in the EAG economic analyses) are based on an efficient level of throughput. This may not hold if centres do not undertake the anticipated number of tests (e.g. in smaller centres, or if multiple tumour profiling tests are available). Furthermore, as NanoString Technologies does not offer a centralised testing service, local testing services will need to be established.

The IHC4 test is not currently commercially available. Standardisation of IHC4 and quality-assurance programmes are required before this test may be used routinely within the NHS.

## Suggested research priorities

- There is uncertainty regarding whether or not *oncotype DX* and *MammaPrint* are predictive of chemotherapy benefit. Further studies that adjust for all relevant clinicopathological factors in validation cohorts are required.
- There is limited evidence demonstrating long-term impacts resulting from the use of the five tumour profiling tests. Future studies assessing the comparative long-term impact of the tests compared with risk prediction tools commonly used in clinical practice would be valuable.
- There is uncertainty regarding the cost-effectiveness of all five tests included in the NICE scope. It is noteworthy that under the assumption of no predictive chemotherapy benefit, the inclusion of additional data collected through the NHS England Access Scheme Database has a significant impact on the conclusions previously drawn from the *oncotype DX* analysis within NICE DG10<sup>20</sup> (moving from an ICER of £22,572 per QALY gained to a situation in which *oncotype DX* is dominated in the LN0 NPI > 3.4 subgroup). Additional UK-based data collection relating to pre- and post-test chemotherapy use for EPClin, IHC4+C, Prosigna and *MammaPrint* may be important in reducing existing uncertainty surrounding the cost-effectiveness of these tests.

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## Contributions of authors

**Sue Harnan** and **Katy Cooper** undertook the clinical evidence review. **Paul Tappenden**, **Alice Bessey**, **Rachid Rafia** and **Sue Ward** undertook the health economic analysis. **John Stevens** provided statistical advice. **Ruth Wong** undertook the literature search. **Robert C Stein** and **Janet Brown** provided clinical advice. All authors were involved in drafting and commenting on the final report.

## About the School of Health and Related Research

The School of Health and Related Research is one of the four schools that constitute the Faculty of Medicine at the University of Sheffield. SchARR brings together a wide range of medical- and health-related disciplines including public health, general practice, mental health, epidemiology, health economics, management sciences, medical statistics, operational research and information science. It includes the Sheffield unit of the Trent Institute for Health Services Research, which is funded by NHS R&D (research and development) to facilitate high-quality health services research and capacity development.

The SchARR Technology Assessment Group (SchARR-TAG) synthesises research on the clinical effectiveness and cost-effectiveness of health-care interventions for the National Institute for Health Research Health Technology Assessment programme on behalf of a range of policy-makers, including NICE. SchARR-TAG is part of a wider collaboration of a number of units from other regions including the Southampton Health Technology Assessment Centre, University of Southampton; Aberdeen Health Technology Assessment Group, University of Aberdeen; Liverpool Reviews & Implementation Group, University of Liverpool; Peninsular Technology Assessment Group, University of Exeter; the NHS CRD, University of York; Warwick Evidence, The University of Warwick; the British Medical Journal Group; and Kleijnen Systematic Reviews.

## Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Please note that exclusive use will be retained until the publication of major outputs. Access to anonymised data may be granted following review.



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## Appendix 1 Additional tables for *Chapter 1*

**TABLE 55** Incidence of breast cancer per 100,000 people in England, by age group and sex (2014)

Age (years)	Sex (n)	
	Male	Female
All	319	45,764
0–24	0	21
25–29	0	191
30–34	4	593
35–39	3	1071
40–44	7	2299
45–49	11	4369
50–54	17	5386
55–59	23	4589
60–64	30	5072
65–69	57	6502
70–74	45	4436
75–79	52	3889
80–84	42	3419
≥ 85	28	3927

**TABLE 56** Breast cancer risk prediction tools

Characteristic	Tool		
	NPI	AOL	Predict
Factors included in prediction algorithm	<ul style="list-style-type: none"> <li>• Tumour size</li> <li>• Nodal status</li> <li>• Tumour grade</li> </ul>	<ul style="list-style-type: none"> <li>• Age at diagnosis</li> <li>• Comorbidity factors</li> <li>• ER status</li> <li>• Tumour size</li> <li>• Tumour grade</li> <li>• Nodal status</li> </ul>	<ul style="list-style-type: none"> <li>• Age at diagnosis</li> <li>• Mode of detection</li> <li>• Tumour size</li> <li>• Tumour grade</li> <li>• Number of positive nodes</li> <li>• ER status</li> <li>• <i>HER2</i> status</li> <li>• Ki-67 status<sup>a</sup></li> <li>• Generation of chemotherapy regimen</li> </ul>
Outcome(s) predicted	Mortality	Mortality or relapse	Mortality

<sup>a</sup> Predict can also be used without Ki-67 status.



## Appendix 2 Literature search strategies

### Clinical effectiveness

#### *Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)*

Date range searched: 1946 to search date.

Search date: 27 February 2017.

#### Search strategy

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#	Searches
1	exp Breast Neoplasms/
2	exp mammary neoplasms/
3	exp "Neoplasms, Ductal, Lobular, and Medullary"/
4	exp breast/
5	exp neoplasms/
6	4 and 5
7	(breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary)).mp.
8	(mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullar)).mp.
9	1 or 2 or 3 or 6 or 7 or 8
10	EndoPredict.mp.
11	myriad genetics.mp.
12	sividon diagnostics.mp.
13	ep score.mp.
14	epclin score.mp.
15	MammaPrint.mp.
16	70-gene.mp.
17	gene70.mp.
18	gene?seventy.mp.
19	seventy?gene.mp.
20	amsterdam profile.mp.
21	oncotype.mp.
22	oncotype dx.mp.
23	21-gene.mp.
24	gene21.mp.
25	gene?twentyone.mp.
26	twentyone?gene.mp.
27	ghi recurrence score.mp.
28	ghi-rs.mp.

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- 
- 29 92-gene.mp.
  - 30 gene92.mp.
  - 31 gene?ninetytwo.mp.
  - 32 ninetytwo?gene.mp.
  - 33 (rct-pcr adj5 "21").mp.
  - 34 prosigna.mp.
  - 35 pam50.mp.
  - 36 50-gene.mp.
  - 37 gene50.mp.
  - 38 gene?fifty.mp.
  - 39 fifty?gene.mp.
  - 40 breast bioclassifier.mp.
  - 41 ihc4.mp.
  - 42 or/10–14
  - 43 or/15–41
  - 44 9 and 42
  - 45 9 and 43
  - 46 limit 45 to yr="2011 -Current"
  - 47 44 or 46
- 

## EMBASE

Date range searched: 1974 to 24 February 2017.

Search date: 27 February 2017.

## Search strategy

---

- # Searches
  - 1 exp breast tumor/
  - 2 exp breast/
  - 3 exp neoplasm/
  - 4 2 and 3
  - 5 (breast\* adj5 (neoplasm\* or cancer\* or tumo?r\* or carcinoma\* or adenocarcinoma\* or sarcoma\* or dcis or ductal or infiltrat\* or intraductal\* or lobular or medullary)).mp.
  - 6 (mammar\* adj5 (neoplasm\* or cancer\* or tumo?r\* or carcinoma\* or adenocarcinoma\* or sarcoma\* or dcis or ductal or infiltrat\* or intraductal\* or lobular or medullar)).mp.
  - 7 1 or 4 or 5 or 6
  - 8 EndoPredict.mp.
  - 9 myriad genetics.mp.
-

---

10 sidon diagnostics.mp.  
11 ep score.mp.  
12 epclin score.mp.  
13 MammaPrint.mp.  
14 70-gene.mp.  
15 gene70.mp.  
16 gene?seventy.mp.  
17 seventy?gene.mp.  
18 amsterdam profile.mp.  
19 oncotype.mp.  
20 oncotype dx.mp.  
21 21-gene.mp.  
22 gene21.mp.  
23 gene?twentyone.mp.  
24 twentyone?gene.mp.  
25 ghi recurrence score.mp.  
26 ghi-rs.mp.  
27 92-gene.mp.  
28 gene92.mp.  
29 gene?ninetytwo.mp.  
30 ninetytwo?gene.mp.  
31 (rct-pcr adj5 "21").mp.  
32 prosigna.mp.  
33 pam50.mp.  
34 50-gene.mp.  
35 gene50.mp.  
36 gene?fifty.mp.  
37 fifty?gene.mp.  
38 breast bioclassifier.mp.  
39 ihc4.mp.  
40 or/8-12  
41 or/13-39  
42 7 and 40  
43 7 and 41  
44 limit 43 to yr="2011 -Current"  
45 42 or 44

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**Web of Science Core Collection databases**

Date range searched: 1900–search date.

Search date: 27 February 2017.

**Science Citation Index Expanded**

Date range searched: 1900–search date.

Search date: 27 February 2017.

**Conference Proceedings Citation Index – Science**

Date range searched: 1900–search date.

Search date: 27 February 2017.

**Search strategy**


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#	Searches
# 1	TOPIC: ((breast* NEAR/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary)))
# 2	TOPIC: ((mammar* NEAR/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary)))
# 3	#2 OR #1
# 4	TOPIC: (EndoPredict) OR TOPIC: (myriad genetics) OR TOPIC: (sividon diagnostics) OR TOPIC: (ep score) OR TOPIC: (epclin score)
# 5	TS=(MammaPrint) OR TS=(70-gene) OR TS=(gene70) OR TS=(gene?seventy) OR TS=(seventy?gene) OR TS=(amsterdam profile)
# 6	TS=(oncotype) OR TS=(oncotype dx) OR TS=(21-gene) OR TS=(gene21) OR TS=(gene?twentyone) OR TS=(twentyone?gene) OR TS=(ghi recurrence score) OR TS=(ghi-rs) OR TS=(92-gene) OR TS=(gene92) OR TS=(gene?ninetytwo) OR TS=(ninetytwo?gene) OR TS=((rct-pcr NEAR/5 '21'))
# 7	TOPIC: (prosigna) OR TOPIC: (pam50) OR TOPIC: (50-gene) OR TOPIC: (gene50) OR TOPIC: (gene?fifty) OR TOPIC: (fifty?gene) OR TOPIC: (breast bioclassifier)
# 8	TOPIC: (ihc4)
# 9	#8 OR #7 OR #6 OR #5
# 10	#9 AND #3 Indexes=SCI-EXPANDED, CPCI-S Timespan=2011–2017
# 11	#4 AND #3
# 12	#11 OR #10

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## Wiley Interscience databases

### Cochrane Database of Systematic Reviews: Wiley Interscience

Date range searched: 1996–search date.

Search date: 28 February 2017.

### Database of Abstracts of Reviews of Effects: Wiley Interscience

Date range searched: 1995–2015.

Search date: 28 February 2017.

### Cochrane Central Register of Controlled Trials: Wiley Interscience

Date range searched: 1995–search date.

Search date: 28 February 2017.

### Health Technology Assessment Database: Wiley Interscience

Date range searched: 1995–2016.

Search date: 28 February 2017.

### NHS Economic Evaluation Database: Wiley Interscience

Date range searched: 1995–2015.

Search date: 28 February 2017.

## Search strategy

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- # Searches
  - #1 MeSH descriptor: [Breast Neoplasms] explode all trees
  - #2 MeSH descriptor: [Neoplasms, Ductal, Lobular, and Medullary] explode all trees
  - #3 MeSH descriptor: [Breast] explode all trees
  - #4 MeSH descriptor: [Neoplasms] explode all trees
  - #5 #3 and #4
  - #6 (breast\* near/5 (neoplasm\* or cancer\* or tumor\* or tumour\* or carcinoma\* or adenocarcinoma\* or sarcoma\* or dcis or ductal or infiltrat\* or intraductal\* or lobular or medullary))
  - #7 (mammar\* near/5 (neoplasm\* or cancer\* or tumor\* or tumour\* or carcinoma\* or adenocarcinoma\* or sarcoma\* or dcis or ductal or infiltrat\* or intraductal\* or lobular or medullar))
  - #8 #1 or #2 or #5 or #6 or #7
  - #9 EndoPredict
  - #10 myriad genetics
  - #11 sividon diagnostics
  - #12 ep score
  - #13 epclin score
  - #14 MammaPrint
  - #15 70-gene
  - #16 gene70
-

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#17	gene*seventy
#18	seventy*gene
#19	amsterdam profile
#20	oncotype
#21	oncotype dx
#22	21-gene
#23	gene21
#24	gene*twentyone
#25	twentyone*gene
#26	ghi recurrence score
#27	ghi-rs
#28	92-gene
#29	gene92
#30	gene*ninetytwo
#31	ninetytwo*gene
#32	(rct-pcr near/5 '21')
#33	prosigna
#34	pam50
#35	50-gene
#36	gene50
#37	gene*fifty
#38	fifty*gene
#39	breast bioclassifier
#40	ihc4
#41	(or #9-#13)
#42	28-#40-#40
#43	#8 and #41
#44	#8 and #42 Publication Year from 2011
#45	#43 or #44

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### ***World Health Organization International Clinical Trials Registry Platform***

Search date: 19 January 2017.

#### **Search strategy**

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#	Searches
1	EndoPredict or MammaPrint or oncotype or IHC4 or Prosigna

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## Cost-effectiveness studies of tumour profiling tests

### *Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)*

Date range searched: 1946 to present.

Search date: 6 March 2017.

### Search strategy

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#	Searches
1	exp Breast Neoplasms/
2	exp mammary neoplasms/
3	exp "Neoplasms, Ductal, Lobular, and Medullary"/
4	exp breast/
5	exp neoplasms/
6	4 and 5
7	(breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary)).mp.
8	(mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullar)).mp.
9	1 or 2 or 3 or 6 or 7 or 8
10	EndoPredict.mp.
11	myriad genetics.mp.
12	sividon diagnostics.mp.
13	ep score.mp.
14	epclin score.mp.
15	MammaPrint.mp.
16	70-gene.mp.
17	gene70.mp.
18	gene?seventy.mp.
19	seventy?gene.mp.
20	amsterdam profile.mp.
21	oncotype.mp.
22	oncotype dx.mp.
23	21-gene.mp.
24	gene21.mp.
25	gene?twentyone.mp.
26	twentyone?gene.mp.
27	ghi recurrence score.mp.
28	ghi-rs.mp.
29	92-gene.mp.
30	gene92.mp.
31	gene?ninetytwo.mp.

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- 32 ninetytwo?gene.mp.  
33 (rct-pcr adj5 '21').mp.  
34 prosigna.mp.  
35 pam50.mp.  
36 50-gene.mp.  
37 gene50.mp.  
38 gene?fifty.mp.  
39 fifty?gene.mp.  
40 breast bioclassifier.mp.  
41 ihc4.mp.  
42 or/10-14  
43 or/15-41  
44 9 and 42  
45 9 and 43  
46 limit 45 to yr="2011 -Current"  
47 44 or 46  
48 exp "Costs and Cost Analysis"/  
49 Economics/  
50 exp Economics, Hospital/  
51 exp Economics, Medical/  
52 Economics, Nursing/  
53 exp models, economic/  
54 Economics, Pharmaceutical/  
55 exp "Fees and Charges"/  
56 exp Budgets/  
57 budget\$.tw.  
58 ec.fs.  
59 cost\$.ti.  
60 (cost\$adj2 (effective\$or utilit\$or benefit\$or minimi\$)).ab.  
61 (economic\$or pharmacoeconomic\$or pharmaco-economic\$).ti.  
62 (price\$or pricing\$).tw.  
63 (financial or finance or finances or financed).tw.  
64 (fee or fees).tw.  
65 (value adj2 (money or monetary)).tw.  
66 quality-adjusted life years/  
67 (qaly or qalys).af.  
68 (quality adjusted life year or quality adjusted life years).af.  
69 or/48-68  
70 47 and 69
-

**EMBASE**

Date range searched: 1974 to 3 March 2017.

Search date: 6 March 2017.

**Search strategy**


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#	Searches
1	exp breast tumor/
2	exp breast/
3	exp neoplasm/
4	2 and 3
5	(breast* adj5 (neoplasm* or cancer* or tumor?* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary)).mp.
6	(mammar* adj5 (neoplasm* or cancer* or tumor?* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullar)).mp.
7	1 or 4 or 5 or 6
8	EndoPredict.mp.
9	myriad genetics.mp.
10	sividon diagnostics.mp.
11	ep score.mp.
12	epclin score.mp.
13	MammaPrint.mp.
14	70-gene.mp.
15	gene70.mp.
16	gene?seventy.mp.
17	seventy?gene.mp.
18	amsterdam profile.mp.
19	oncotype.mp.
20	oncotype dx.mp.
21	21-gene.mp.
22	gene21.mp.
23	gene?twentyone.mp.
24	twentyone?gene.mp.
25	ghi recurrence score.mp.
26	ghi-rs.mp.
27	92-gene.mp.
28	gene92.mp.
29	gene?ninetytwo.mp.
30	ninetytwo?gene.mp.

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- 
- 31 (rct-pcr adj5 '21').mp.
  - 32 prosigna.mp.
  - 33 pam50.mp.
  - 34 50-gene.mp.
  - 35 gene50.mp.
  - 36 gene?fifty.mp.
  - 37 fifty?gene.mp.
  - 38 breast bioclassifier.mp.
  - 39 ihc4.mp.
  - 40 or/8-12
  - 41 or/13-39
  - 42 7 and 40
  - 43 7 and 41
  - 44 limit 43 to yr="2011 -Current"
  - 45 42 or 44
  - 46 Socioeconomics/
  - 47 Cost benefit analysis/
  - 48 Cost effectiveness analysis/
  - 49 Cost of illness/
  - 50 Cost control/
  - 51 Economic aspect/
  - 52 Financial management/
  - 53 Health care cost/
  - 54 Health care financing/
  - 55 Health economics/
  - 56 Hospital cost/
  - 57 (fiscal or financial or finance or funding).tw.
  - 58 Cost minimization analysis/
  - 59 (cost adj estimate\$).mp.
  - 60 (cost adj variable\$).mp.
  - 61 (unit adj cost\$).mp.
  - 62 or/46-61
  - 63 45 and 62
-

### Web of Science Core Collection databases

Date range searched: 1900–search date.

Search date: 6 March 2017.

### Science Citation Index Expanded

Date range searched: 1900–search date.

Search date: 6 March 2017.

### Conference Proceedings Citation Index – Science

Date range searched: 1900–search date.

Search date: 6 March 2017.

### Search strategy

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#	Searches
# 1	TOPIC: ((breast* NEAR/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary)))
# 2	TOPIC: ((mammar* NEAR/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullar)))
# 3	#2 OR #1
# 4	TOPIC: (EndoPredict) OR TOPIC: (myriad genetics) OR TOPIC: (sividon diagnostics) OR TOPIC: (ep score) OR TOPIC: (epclin score)
# 5	TS=(MammaPrint) OR TS=(70-gene) OR TS=(gene70) OR TS=(gene?seventy) OR TS=(seventy?gene) OR TS=(amsterdam profile)
# 6	TS=(oncotype) OR TS=(oncotype dx) OR TS=(21-gene) OR TS=(gene21) OR TS=(gene?twentyone) OR TS=(twentyone?gene) OR TS=(ghi recurrence score) OR TS=(ghi-rs) OR TS=(92-gene) OR TS=(gene92) OR TS=(gene?ninetytwo) OR TS=(ninetytwo?gene) OR TS=((rct-pcr NEAR/5 '21'))
# 7	TOPIC: (prosigna) OR TOPIC: (pam50) OR TOPIC: (50-gene) OR TOPIC: (gene50) OR TOPIC: (gene?fifty) OR TOPIC: (fifty?gene) OR TOPIC: (breast bioclassifier)
# 8	TOPIC: (ihc4)
# 9	#8 OR #7 OR #6 OR #5
# 10	#9 AND #3 Indexes=SCI-EXPANDED, CPCI-S Timespan=2011-2017
# 11	#4 AND #3
# 12	#11 OR #10
# 13	TS=(cost* and (effective* or utilit* or benefit* or minimi*)) OR TS=(cost*) OR TI=(economic* or pharmaco-economic* or pharmaco-economic*) OR TS=(price* or pricing*) OR TS=(financial or finance or finances or financed) OR TS=(fee or fees) OR TS=(value and (money or monetary)) OR TS=(economic*) OR TS=(economic* and (hospital or medical or nursing or pharmaceutical)) OR TS=("quality adjusted life year" or "quality adjusted life years") OR TS=(qaly or qalys) OR TS=(budget*)
# 14	#13 AND #12

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**Health Technology Assessment Database: Wiley Interscience**

Date range searched: 1995–2016.

Search date: 7 March 2017.

**NHS Economic Evaluation Database: Wiley Interscience**

Date range searched: 1995–2015.

Search date: 7 March 2017.

**Search strategy**


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#	Searches
1	MeSH DESCRIPTOR Breast Neoplasms EXPLODE ALL TREES
2	MeSH DESCRIPTOR Neoplasms, Ductal, Lobular, and Medullary EXPLODE ALL TREES
3	MeSH DESCRIPTOR Breast EXPLODE ALL TREES
4	MeSH DESCRIPTOR Neoplasms EXPLODE ALL TREES
5	#3 AND #4
6	((breast* ADJ5 (neoplasm* or cancer* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary)))
7	((mammar* ADJ5 (neoplasm* or cancer* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullar)))
8	#1 OR #2 OR #5 OR #6 OR #7
9	(EndoPredict or myriad genetics or sividon diagnostics or ep score or epclin score)
10	(MammaPrint or 70-gene or gene70 or gene*seventy or seventy*gene or amsterdam profile)
11	(oncotype or oncotype dx or 21-gene or gene21 or gene*twentyone or twentyone*gene or ghi recurrence score or ghi-rs or 92-gene or gene92 or gene*ninetytwo or ninetytwo*gene or (rct-pcr ADJ5 '21'))
12	(prosigna or pam50 or 50-gene or gene50 or gene*fifty or fifty*gene or breast bioclassifier)
13	(ihc4)
14	#8 AND #9
15	#10 OR #11 OR #12 OR #13
16	(#8 AND #15) FROM 2011 TO 2017
17	(#8 AND #15) IN HTA FROM 2011 TO 2017
18	(#8 AND #15) IN NHSEED FROM 2011 TO 2017

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## Cost-effectiveness reviews for breast cancer

### *Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)*

Date range searched: 1946 to present.

Search date: 7 March 2017.

### Search strategy

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#	Searches
1	exp Breast Neoplasms/
2	exp mammary neoplasms/
3	exp "Neoplasms, Ductal, Lobular, and Medullary"/
4	exp breast/
5	exp neoplasms/
6	4 and 5
7	(breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary)).ti.
8	(mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullar)).ti.
9	1 or 2 or 3 or 6 or 7 or 8
10	exp "Costs and Cost Analysis"/
11	Economics/
12	exp Economics, Hospital/
13	exp Economics, Medical/
14	Economics, Nursing/
15	exp models, economic/
16	Economics, Pharmaceutical/
17	exp "Fees and Charges"/
18	exp Budgets/
19	budget\$.tw.
20	ec.fs.
21	cost\$.ti.
22	(cost\$adj2 (effective\$or utilit\$or benefit\$or minimi\$)).ab.
23	(economic\$or pharmacoeconomic\$or pharmaco-economic\$).ti.
24	(price\$or pricing\$).tw.
25	(financial or finance or finances or financed).tw.
26	(fee or fees).tw.
27	(value adj2 (money or monetary)).tw.
28	quality-adjusted life years/

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- 
- 29 (qaly or qalys).af.  
 30 (quality adjusted life year or quality adjusted life years).af.  
 31 or/10-30  
 32 9 and 31  
 33 meta-analysis/  
 34 meta-analysis as topic/  
 35 (meta analy\* or metanaly\* or metaanaly\*).ti,ab.  
 36 ((systematic\* or evidence\*) adj3 (review\* or overview\*)).ti,ab.  
 37 (reference list\* or bibliograph\* or hand search\* or manual search\* or relevant journals).ab.  
 38 (search strategy or search criteria or systematic search or study selection or data extraction).ab.  
 39 (search\* adj4 literature).ab.  
 40 (medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or scie nce citation index or bids or cancerlit).ab.  
 41 cochrane.jw.  
 42 ((multiple treatment\* or indirect or mixed) adj2 comparison\*).ti,ab.  
 43 or/33-42  
 44 32 and 43  
 45 limit 44 to yr="2011 -Current"
- 

## EMBASE

Date range searched: 1974 to 6 March 2017.

Search date: 7 March 2017.

### Search strategy

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- | #  | Searches  |
|----|---|
| 1  | exp breast tumor/   |
| 2  | exp breast/   |
| 3  | exp neoplasm/   |
| 4  | 2 and 3   |
| 5  | (breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary)).ti. |
| 6  | (mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullar)).ti.  |
| 7  | 1 or 4 or 5 or 6  |
| 8  | Socioeconomics/   |
| 9  | Cost benefit analysis/  |
| 10 | Cost effectiveness analysis/  |
| 11 | Cost of illness/  |
-

- 
- 12 Cost control/
  - 13 Economic aspect/
  - 14 Financial management/
  - 15 Health care cost/
  - 16 Health care financing/
  - 17 Health economics/
  - 18 Hospital cost/
  - 19 (fiscal or financial or finance or funding).tw.
  - 20 Cost minimization analysis/
  - 21 (cost adj estimate\$).mp.
  - 22 (cost adj variable\$).mp.
  - 23 (unit adj cost\$).mp.
  - 24 or/8-23
  - 25 7 and 24
  - 26 systematic review/
  - 27 meta-analysis/
  - 28 (meta analy\* or metanaly\* or metaanaly\*).ti,ab.
  - 29 ((systematic or evidence) adj3 (review\* or overview\*)).ti,ab.
  - 30 (reference list\* or bibliograph\* or hand search\* or manual search\* or relevant journals).ab.
  - 31 (search strategy or search criteria or systematic search or study selection or data extraction).ab.
  - 32 (search\* adj4 literature).ab.
  - 33 (medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
  - 34 cochrane.jw.
  - 35 ((multiple treatment\* or indirect or mixed) adj2 comparison\*).ti,ab.
  - 36 or/26-35
  - 37 25 and 36
  - 38 limit 37 to yr="2011 -Current"
-

**Web of Science Core Collection databases**

Date range searched: 1900–search date.

Search date: 7 March 2017.

**Science Citation Index Expanded**

Date range searched: 1900–search date.

Search date: 7 March 2017.

**Conference Proceedings Citation Index – Science**

Date range searched: 1900–search date.

Search date: 7 March 2017.

**Search strategy**


---

#	Searches
# 1	TI=((breast* NEAR/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary)))
# 2	TI=((mammar* NEAR/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullar)))
# 3	#2 OR #1
# 4	TS=(cost* and (effective* or utilit* or benefit* or minimi*)) OR TS=(cost*) OR TI=(economic* or pharmaco-economic* or pharmaco-economic*) OR TS=(price* or pricing*) OR TS=(financial or finance or finances or financed) OR TS=(fee or fees) OR TS=(value and (money or monetary)) OR TS=(economic*) OR TS=(economic* and (hospital or medical or nursing or pharmaceutical)) OR TS=("quality adjusted life year" or "quality adjusted life years") OR TS=(qaly or qalys) OR TS=(budget*)
# 5	#4 AND #3
# 6	TS=(meta-analysis or meta analy* or metaanaly*) OR TS=("review literature" or "literature review") OR TS=("systematic review*" or "systematic overview*") OR TS=(cochrane or embase or psychlit or psychlit or psychinfo or psycinfo or cinahl or cinhal or science citation index or bids or cancerlit) OR TS=("reference list*" or bibliograph* or hand-search* or "relevant journals" or "manual search*") OR TS(("selection criteria" or "data extraction") and review)
# 7	#6 AND #5 Indexes=SCI-EXPANDED, CPCI-S Timespan=2011-2017

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**Health Technology Assessment Database: Centre for Reviews and Dissemination**

Date range searched: 1995–2016.

Search date: 7 March 2017.

**NHS Economic Evaluation Database: Centre for Reviews and Dissemination**

Date range searched: 1995–2015.

Search date: 7 March 2017.

**Search strategy**


---

#	Searches
1	MeSH DESCRIPTOR Breast Neoplasms EXPLODE ALL TREES
2	MeSH DESCRIPTOR Neoplasms, Ductal, Lobular, and Medullary EXPLODE ALL TREES
3	MeSH DESCRIPTOR Breast EXPLODE ALL TREES
4	MeSH DESCRIPTOR Neoplasms EXPLODE ALL TREES
5	#3 AND #4
6	((breast* ADJ5 (neoplasm* or cancer* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary)))
7	((mammar* ADJ5 (neoplasm* or cancer* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullar)))
8	#1 OR #2 OR #5 OR #6 OR #7
9	(EndoPredict or myriad genetics or sividon diagnostics or ep score or epcin score)
10	(MammaPrint or 70-gene or gene70 or gene*seventy or seventy*gene or amsterdam profile)
11	(oncotype or oncotype dx or 21-gene or gene21 or gene*twentyone or twentyone*gene or ghi recurrence score or ghi-rs or 92-gene or gene92 or gene*ninetytwo or ninetytwo*gene or (rct-pcr ADJ5 '21'))
12	(prosigna or pam50 or 50-gene or gene50 or gene*fifty or fifty*gene or breast bioclassifier)
13	(ihc4)
14	#8 AND #9
15	#10 OR #11 OR #12 OR #13
16	(#8 AND #15) FROM 2011 TO 2017
17	(#8 AND #15) IN HTA FROM 2011 TO 2017
18	(#8 AND #15) IN NHSEED FROM 2011 TO 2017

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## Quality-of-life reviews for breast cancer

### *Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)*

Date range searched: 1946 to present.

Search date: 7 March 2017.

### Search strategy

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#	Searches
1	exp Breast Neoplasms/
2	exp mammary neoplasms/
3	exp "Neoplasms, Ductal, Lobular, and Medullary"/
4	exp breast/
5	exp neoplasms/
6	4 and 5
7	(breast* adj5 (neoplasm* or cancer* or tumor* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary)).ti.
8	(mammar* adj5 (neoplasm* or cancer* or tumor* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullar)).ti.
9	1 or 2 or 3 or 6 or 7 or 8
10	"Quality of Life"/
11	(qol or (quality adj2 life)).ab,ti.
12	(value adj2 (money or monetary)).tw.
13	value of life/
14	quality adjusted life year/
15	quality adjusted life.tw.
16	(qaly\$or qald\$or qale\$or qtime\$).tw.
17	disability adjusted life.tw.
18	daly\$.tw.
19	health status indicators/
20	(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
21	(sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
22	(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
23	(sf6D or sf 6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D).tw.
24	(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
25	(euroqol or euro qol or eq5d or eq 5d).tw.
26	(hql or hqol or h qol or hrqol or hr qol).tw.
27	(hye or hyes).tw.

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- 28 health\$year\$equivalent\$.tw.  
29 health utilit\$.tw.  
30 (hui or hui1 or hui2 or hui3).tw.  
31 disutilit\$.tw.  
32 rosser.tw.  
33 (quality adj2 wellbeing).tw.  
34 qwb.tw.  
35 (willingness adj2 pay).tw.  
36 standard gamble\$.tw.  
37 time trade off.tw.  
38 time tradeoff.tw.  
39 tto.tw.  
40 letter.pt.  
41 editorial.pt.  
42 comment.pt.  
43 40 or 41 or 42  
44 or/10-39  
45 44 not 43  
46 9 and 45  
47 meta-analysis/  
48 meta-analysis as topic/  
49 (meta analy\* or metanaly\* or metaanaly\*).ti,ab.  
50 ((systematic\* or evidence\*) adj3 (review\* or overview\*)).ti,ab.  
51 (reference list\* or bibliograph\* or hand search\* or manual search\* or relevant journals).ab.  
52 (search strategy or search criteria or systematic search or study selection or data extraction).ab.  
53 (search\* adj4 literature).ab.  
54 (medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or scie nce citation index or bids or cancerlit).ab.  
55 cochrane.jw.  
56 ((multiple treatment\* or indirect or mixed) adj2 comparison\*).ti,ab.  
57 or/47-56  
58 46 and 57  
59 limit 58 to yr="2011 -Current"
-

**EMBASE**

Date range searched: 1974 to 6 March 2017.

Search date: 7 March 2017.

**Search strategy**


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#	Searches
1	exp breast tumor/
2	exp breast/
3	exp neoplasm/
4	2 and 3
5	(breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary)).ti.
6	(mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullar)).ti.
7	1 or 4 or 5 or 6
8	socioeconomics/
9	quality adjusted life year/
10	quality adjusted life.tw.
11	(qaly\$or qald\$or qale\$or qtime\$).tw.
12	disability adjusted life.tw.
13	daly\$.tw.
14	health survey/
15	(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
16	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
17	(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
18	(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
19	(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
20	(euroqol or euro qol or eq5d or eq 5d).tw.
21	(hql or hqol or h qol or hrqol or hr qol).tw.
22	(hye or hyes).tw.
23	health\$year\$equivalent\$.tw.
24	health utilit\$.tw.
25	(hui or hui1 or hui2 or hui3).tw.
26	disutili\$.tw.
27	rosser.tw.
28	quality of wellbeing.tw.
29	qwb.tw.
30	willingness to pay.tw.
31	standard gamble\$.tw.

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- 32 time trade off.tw.  
 33 time tradeoff.tw.  
 34 tto.tw.  
 35 or/8-34  
 36 7 and 35  
 37 systematic review/  
 38 meta-analysis/  
 39 (meta analy\* or metanaly\* or metaanaly\*).ti,ab.  
 40 ((systematic or evidence) adj3 (review\* or overview\*)).ti,ab.  
 41 (reference list\* or bibliograph\* or hand search\* or manual search\* or relevant journals).ab.  
 42 (search strategy or search criteria or systematic search or study selection or data extraction).ab.  
 43 (search\* adj4 literature).ab.  
 44 (medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.  
 45 cochrane.jw.  
 46 ((multiple treatment\* or indirect or mixed) adj2 comparison\*).ti,ab.  
 47 or/37-46  
 48 36 and 47  
 49 limit 48 to yr="2011 -Current"
- 

### **Web of Science Core Collection databases**

Date range searched: 1900–search date.

Search date: 7 March 2017.

### **Science Citation Index Expanded**

Date range searched: 1900–search date.

Search date: 7 March 2017.

### **Conference Proceedings Citation Index – Science**

Date range searched: 1900–search date.

Search date: 7 March 2017.

### **Search strategy**

- 
- | #   | Searches   |
|-----|--|
| # 1 | TI=((breast* NEAR/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary))) |
| # 2 | TI=((mammar* NEAR/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullar)))  |
| # 3 | #2 OR #1   |
-

- 
- # 4 TS=(qol or "quality of life" or "quality adjusted life" or qaly\* or qald\* or qale\* or qtime\* or "disability adjusted life" or daly\*)OR TS=(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six) OR TS=(sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six) OR TS=(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve) OR TS=(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen) OR TS=(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty) OR TS=(euroqol or euro qol or eq5d or eq 5d or hql or hqol or h qol or hrqol or hr qol or disutilit\* or rosser "quality of wellbeing" or qwb or "willingness to pay" or "standard gamble\*" or "time trade off" or "time tradeoff" or tto)
- # 5 #4 AND #3
- # 6 TS=(meta-analysis or meta analy\* or metaanaly\*) OR TS=("review literature" or "literature review") OR TS=("systematic review\*" or "systematic overview\*") OR TS=(cochrane or embase or psychlit or psychlit or psychinfo or psycinfo or cinahl or cinhal or science citation index or bids or cancerlit) OR TS=("reference list\*" or bibliograph\* or hand-search\* or "relevant journals" or "manual search\*") OR TS=(("selection criteria" or "data extraction") and review)
- # 7 #6 AND #5
- Indexes=SCI-EXPANDED, CPCI-S Timespan=2011-2017
- 

### **Health Technology Assessment Database: Centre for Reviews and Dissemination**

Date range searched: 1995–2016.

Search date: 7 March 2017.

### **NHS Economic Evaluation Database: Centre for Reviews and Dissemination**

Date range searched: 1995–2015.

Search date: 7 March 2017.

### **Search strategy**

- 
- # Searches
- 1 MeSH DESCRIPTOR Breast Neoplasms EXPLODE ALL TREES
  - 2 MeSH DESCRIPTOR Neoplasms, Ductal, Lobular, and Medullary EXPLODE ALL TREES
  - 3 MeSH DESCRIPTOR Breast EXPLODE ALL TREES
  - 4 MeSH DESCRIPTOR Neoplasms EXPLODE ALL TREES
  - 5 #3 AND #4
  - 6 (((breast\* ADJ5 (neoplasm\* or cancer\* or tumor\* or tumour\* or carcinoma\* or adenocarcinoma\* or sarcoma\* or dcis or ductal or infiltrat\* or intraductal\* or lobular or medullary)))):TI
  - 7 (((mammar\* ADJ5 (neoplasm\* or cancer\* or tumor\* or tumour\* or carcinoma\* or adenocarcinoma\* or sarcoma\* or dcis or ductal or infiltrat\* or intraductal\* or lobular or medullar)))):TI
  - 8 #1 OR #2 OR #5 OR #6 OR #7
  - 9 (#8) IN HTA FROM 2011 TO 2017
  - 10 (#8) IN NHSEED FROM 2011 TO 2017
-

## EuroQol 5-Dimensions and breast cancer

### *Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)*

Date range searched: 1946 to present.

Search date: 10 July 2017.

#### Search strategy

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- |    |   |
|----|---|
| #  | Searches  |
| 1  | exp Breast Neoplasms/   |
| 2  | exp mammary neoplasms/  |
| 3  | exp "Neoplasms, Ductal, Lobular, and Medullary"/  |
| 4  | exp breast/   |
| 5  | exp neoplasms/  |
| 6  | 4 and 5   |
| 7  | (breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary)).ti. |
| 8  | (mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullar)).ti.  |
| 9  | 1 or 2 or 3 or 6 or 7 or 8  |
| 10 | (euroqol or euro qol or eq5d or eq 5d).tw.  |
| 11 | 9 and 10  |
- 

### **EMBASE**

Date range searched: 1974 to 7 July 2017.

Search date: 10 July 2017.

#### Search strategy

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- |   |   |
|---|---|
| # | Searches  |
| 1 | exp breast tumor/   |
| 2 | exp breast/   |
| 3 | exp neoplasm/   |
| 4 | 2 and 3   |
| 5 | (breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary)).ti. |
| 6 | (mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullar)).ti.  |
| 7 | 1 or 4 or 5 or 6  |
| 8 | (euroqol or euro qol or eq5d or eq 5d).tw.  |
| 9 | 7 and 8   |
-

**Web of Science Core Collection databases**

Date range searched: 1900–search date.

Search date: 10 July 2017.

**Science Citation Index Expanded**

Date range searched: 1900–search date.

Search date: 10 July 2017.

**Conference Proceedings Citation Index – Science**

Date range searched: 1900–search date.

Search date: 10 July 2017.

**Search strategy**


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#	Searches
# 1	TI=((breast* NEAR/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary)))
# 2	TI=((mammar* NEAR/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullar)))
# 3	#2 OR #1
# 4	TOPIC: (euroqol or euro qol or eq5d or eq 5d)
# 5	#4 AND #3

---

## Appendix 3 Table of excluded studies with rationale

Type of exclusion	Reason for exclusion	References
Population exclusions	<ul style="list-style-type: none"> <li>• More than three lymph nodes</li> <li>• Advanced breast cancer</li> <li>• Neoadjuvant setting</li> <li>• Not breast cancer</li> <li>• Non-European (for decision impact studies)</li> </ul>	40 <sup>176,210–248</sup>
Intervention exclusions	<ul style="list-style-type: none"> <li>• Not in-scope test</li> </ul>	27 <sup>249–275</sup>
Comparator exclusions	<ul style="list-style-type: none"> <li>• Not in-scope comparator</li> </ul>	3 <sup>276–278</sup>
Outcome exclusions	<ul style="list-style-type: none"> <li>• No outcomes of interest</li> <li>• Follow-up of &lt; 5 years</li> <li>• Insufficient data</li> <li>• Pooled analysis (where individual studies are included)</li> <li>• Correlation only</li> <li>• Analytic validity only</li> </ul>	146 <sup>279–424</sup>
Study type exclusions	<ul style="list-style-type: none"> <li>• Not in English language</li> <li>• Editorial or comment</li> <li>• Systematic review</li> <li>• Modelling</li> <li>• Review</li> <li>• Retrospective use of test</li> </ul>	34 <sup>121,425–457</sup>
Other reasons for exclusions	<ul style="list-style-type: none"> <li>• Could not obtain full text</li> <li>• No novel data (secondary reference to other study)</li> </ul>	2 <sup>458,459</sup> 128 <sup>460–586</sup>



## Appendix 4 Summary of the clinical review

This appendix provides a summary of results for all included tests, ordered by type of evidence.

For the sake of clarity, this section focuses on LN0 and LN+ subgroups only, DRFI/DRFS outcomes and key points. Full descriptions and discussions of the evidence base are reported in *Chapter 2, Report Supplementary Material 1–10*, and *Appendix 5*, and should be read in conjunction with this summary to obtain a full understanding. The derivation cohorts are excluded from the summary (i.e. three US cohorts for oncotype DX,<sup>49</sup> TransATAC<sup>46</sup> for IHC4 and IHC4+C, TransATAC and NSABP B-14 pooled<sup>44</sup> for RSPC, van 't Veer *et al.*<sup>587</sup> for MammaPrint, van de Vijver *et al.*<sup>79</sup> for Prosigna and Filipits *et al.*<sup>117</sup> for EndoPredict), except in the case of IHC4+C, as only the derivation data reported numerical values.

### Risk classification

#### Lymph node negative

Among studies of LN0 patients receiving endocrine monotherapy, percentages categorised as high risk ranged from 9% to 33% across all five tests (*Table 57*): 9–33% for oncotype DX (three studies<sup>46,49,50,52,60,61</sup>), 29% for MammaPrint (one study<sup>91</sup>), 15–20% for Prosigna/ROR-PT (three studies<sup>46,104,105,112</sup>), 27% for EPclin (one study<sup>46,118–120</sup>), 9% for IHC4+C (derivation cohort<sup>46</sup>) and not reported for IHC4. Within studies with variable endocrine therapy and chemotherapy use, percentages categorised as high risk were similar to the above for oncotype DX (25–28%), but higher for MammaPrint (33–73%); this may reflect the selection of higher-risk patients for MammaPrint studies (some not ER+, some required chemotherapy).

#### Lymph node positive

Three tests (Prosigna/ROR-PT, EPclin and IHC4+C) categorised far more LN+ than LN0 patients as high risk among studies of endocrine monotherapy (see *Table 57*): 48–62% for Prosigna/ROR-PT (three studies<sup>46,104,105,112</sup>), 76% for EPclin (one study<sup>46,118–120</sup>) and 38% for IHC4+C (one study<sup>46</sup>). Conversely, oncotype DX categorised similar percentages of LN+ and LN0 patients as high risk (11% for LN+; one study<sup>46</sup>). For MammaPrint, there were no LN+ endocrine monotherapy studies, but in studies with variable endocrine therapy and chemotherapy use, 59–62% were high risk (two studies<sup>85,89</sup>); this was similar to LN0 studies.

For tests with three categories, how many patients would be prescribed chemotherapy would depend on how intermediate patients are handled (see *Table 57*).

### Prognostic performance and additional prognostic value

#### Oncotype DX

Seven reanalyses of RCTs<sup>37,46,49–56</sup> and four retrospective cohort studies<sup>57–60</sup> were included (total  $n = 4929$ ). The 10-year DRFI rates for LN0 low-risk patients were 93–97% (with endocrine monotherapy); for intermediate-risk patients they were somewhat higher (86–100%). LN+ patients were generally at higher risk of recurrence than LN0 patients in both low and intermediate categories (10-year DRFI for LN+ was < 85% for low-risk patients and  $\leq 75%$  for intermediate-risk patients). Unadjusted analyses indicated that oncotype DX was prognostic (statistically significant differences between low-risk and high-risk groups) across various recurrence outcomes regardless of lymph node status, although HRs between intermediate-risk and high- or low-risk groups were not always statistically significant. Oncotype DX provided additional prognostic information over most commonly used clinicopathological variables (age, grade, size and nodal status) regardless of lymph node status, and over CTS and NPI in LN0 (but not LN+) patients, but analyses used a 50-point or 1-point difference rather than categories defined by the 18–30 cut-off points.

**TABLE 57** Summary of risk categorisation and prognostic and predictive (of chemotherapy benefit) ability across tests

Test	Number of studies with DRFS/DRFI	Population	Nodal status	ET/chemotherapy	Percentage of patients per group			Percentage with 10-year DRFS/DRFI risk			Significantly prognostic for DRFS/DRFI?	Additional value over clinicopathological factors or tests? <sup>a</sup>	Chemotherapy benefit?
					Low risk	Intermediate risk	High risk	Low risk	Intermediate risk	High risk			
<b>LN0, all ET, no chemotherapy</b>													
Oncotype DX	3 <sup>46,49,52,60,61</sup>	ER+; HER2+/-	LN0	All ET; no chemotherapy	48–64	20–27	9–33	93–97	86–100	70–77	Yes (3 of 4 studies, NR in 1)	Yes (3 studies)	Weak <sup>b</sup>
MammaPrint	1 <sup>91</sup>	ER+; HER2 NR	LN0	All ET; no chemotherapy	71	–	29	93	–	85	NR	NR	
Prosigna/ROR-PT	3 <sup>46,104,105,112</sup>	Most ER+; HER2–	LN0	All ET; no chemotherapy	48–55	30–32	15–20	95–97	87–93	69–85	Yes (3 of 3 studies)	Yes vs. CTS and NPI (2 studies)	N/A
EPClin	1 <sup>46,118–120</sup>	ER+; HER2–	LN0	All ET; no chemotherapy	73	–	27	94	–	80	Yes (1 study)	Yes vs. CTS and NPI (1 study)	N/A
IHC4	2 cohorts <sup>126</sup>	ER+; HER2– NR	LN0	All ET; no chemotherapy	NR	NR	NR	NR	NR	NR	NR	Yes (2 cohorts)	N/A
IHC4+C	1 <sup>46</sup> (derivation)	ER+; 95% HER2–	LN0	All ET; no chemotherapy	70	21	9	96	82	77	Yes (1 study)	Yes vs. CTS and NPI (1 study)	N/A
<b>LN0, variable ET/chemotherapy</b>													
Oncotype DX	2 <sup>50,58</sup>	ER+; HER2+/-	LN0	75–100% ET; 79–100% chemotherapy	49–51	21–26	25–28	96 <sup>50</sup>	89 <sup>50</sup>	88 <sup>50</sup>	Yes (1 of 1 study)	NR	NR
Oncotype DX RSPC	1 <sup>44</sup>	ER+; HER2– NR	LN0	All ET; 64% chemotherapy	NR	NR	NR	NR	NR	NR	Yes (1 analysis)	Yes (derivation set)	No (1 study)
MammaPrint	7 <sup>79,84,86,88,91,95,96</sup>	70–100% ER+; HER2 NR	LN0	0–25% ET/ chemotherapy	27–67	–	33–73	80–90	–	50–71	Yes (4 of 7 studies, 1 not significant, NR in 2)	Yes (pooled study, 2 cohorts, others NR)	Not statistically significant (pooled LN0/LN+) <sup>b</sup>
IHC4	2 <sup>125,127</sup>	ER/HER2 varies		Some ET/ chemotherapy	Clinical cut-off points not used			NR	NR	NR	Yes (some analyses non-significant)	NR	N/A

Test	Number of studies with DRFS/DRFI	Population	Nodal status	ET/chemotherapy	Percentage of patients per group			Percentage with 10-year DRFS/DRFI risk			Significantly prognostic for DRFS/DRFI?	Additional value over clinicopathological factors or tests? <sup>a</sup>	Chemotherapy benefit?
					Low risk	Intermediate risk	High risk	Low risk	Intermediate risk	High risk			
<b>LN+, all ET, no chemotherapy</b>													
Oncotype DX	1 <sup>46</sup>	ER+; HER2-	LN1-3	All ET; no chemotherapy	57	32	11	82	75	67	Yes (1 study)	No vs. CTS and NPI	Weak <sup>b</sup>
Prosigna/ROR-PT	3 <sup>46,104,105,112</sup>	Most ER+; HER2-	LN1-3 (most)	All ET; no chemotherapy	4-25	27-34	48-62	100-100	81-94	71-78	Yes or borderline (3 studies)	Yes vs. CTS, no vs. NPI	NR
EPclin	1 <sup>46,118-120</sup>	ER+; HER2-	LN1-3	All ET; no chemotherapy	24	-	76	95	-	72	Yes (1 study)	Yes vs. CTS and NPI at 10 years (not 5 years)	NR
IHC4	2 cohorts <sup>126</sup>	ER+; HER2- NR	LN+	All ET; no chemotherapy	NR			NR			NR	Mixed (1 yes, 1 no)	NR
IHC4+C <sup>d</sup>	1 <sup>46</sup>	ER+; HER2-	LN1-3	All ET; no chemotherapy	28	34	38	96	75	67	Yes (1 study)	No vs. CTS and NPI	NR
<b>LN+, variable ET/chemotherapy</b>													
Oncotype DX	3 <sup>51,52,56,59</sup>	ER+; HER2+/-	LN+	74-100% ET/ chemotherapy	36-39	30-34	30-31	81 <sup>e</sup>	65 <sup>e</sup>	59 <sup>e</sup>	Yes	Yes	N/A
MammaPrint	2 <sup>85,89</sup>	80% ER+; 84% HER2 or NR	LN1-3; LN > 3, 26%	Some ET/ chemotherapy	38-41	-	59-62	79-91		54-76	Yes (2 of 2 studies)	Borderline (1 study)	Not statistically significant (pooled LN0/LN+) <sup>b</sup>
Prosigna/ROR-PT	1 <sup>108,109</sup>	ER+; HER2-	LN > 3, 36%	All ET; all chemotherapy	19	56	26	92	74	66	Yes (1 study)	NR	NR
EPclin	1 <sup>108,109</sup>	ER+; HER2-	LN > 3, 36%	All ET; all chemotherapy	13	-	87	100		72	Yes (1 study)	NR	NR
IHC4	2 <sup>123,136</sup>	HR+; HER2-	LN+	ET varies; 100% chemotherapy	Clinical cut-off points not used			No clinical groups			NR	Mixed (1 yes, 1 no)	NR

ET, endocrine therapy; N/A, not applicable; NR, not reported.

<sup>a</sup> Judged via multivariate analyses adjusted for clinicopathological factors, change in likelihood ratios, C-index or D-statistics.

<sup>b</sup> Judged via *p* values and non-significant interaction tests after adjustments for clinicopathological factors.

<sup>c</sup> Where an outlier, Ishitobi *et al.*<sup>95</sup> (Japan) omitted owing to unknown generalisability.

<sup>d</sup> For IHC alone, there were few data by LN status.

<sup>e</sup> Sun *et al.*<sup>59</sup> (China) omitted, as much lower DRFS than other studies.

### **Oncotype DX RSPC**

One study<sup>44</sup> derived the RSPC score in a meta-analysis of two RCT data sets (LN0/LN+;  $n = 1735$ ) and validated it in another (LN0;  $n = 625$ ), which included 233 patients used to derive the *oncotype* DX Breast Recurrence Score. Based on the derivation analysis set, the *oncotype* DX RSPC algorithm (*oncotype* DX plus age, tumour size and grade) appeared to provide additional prognostic information over *oncotype* DX and over clinicopathological variables, and was able to classify more patients into a low-risk category than *oncotype* DX while maintaining a roughly equivalent rate of distant recurrence in the low-risk group. In the validation cohort, RSPC had prognostic value in univariate analyses (no adjusted analysis was reported). However, RSPC has only been validated in one independent cohort that included patients who were used to derive one of its constituent parts (*oncotype* DX Breast Recurrence Score), and has not been tested in premenopausal or LN+ patients.

### **MammaPrint**

The prognostic value of MammaPrint is based on nine retrospective analyses (total  $n = 1805$ ), four pooled analyses ( $n = 964$ ; including six of the nine series above) and one reanalysis of a RCT ( $n = 538$ ). Studies were variable in terms of nodal status, ER status and receipt of endocrine therapy and chemotherapy. MammaPrint was statistically significantly prognostic for 10-year DRFS in almost all unadjusted analyses of LN0 and LN+ patients. For LN0 patients, 10-year DRFS/DRFI rates for low-risk patients ranged from 80% to 90% (with varying rates of endocrine therapy and chemotherapy use), while the reanalysis of a RCT reported 10-year DRFS of 93% with endocrine monotherapy and 83% without endocrine therapy or chemotherapy. For LN+ patients, 10-year DRFS rates in low-risk patients ranged from 79% to 91% (with varying rates of endocrine therapy and chemotherapy use). In terms of additional prognostic value, MammaPrint was statistically significantly prognostic for 10-year DRFS/DRFI in multivariable analyses adjusted for clinicopathological risk tools (AOL and NPI) and various combinations of clinicopathological variables in LN0/LN+ and LN0 cohorts, while adjusted analyses in LN+ cohorts were statistically significant or borderline significant.

### **Prosigna/risk of recurrence based on Prediction Analysis of Microarray 50 subtype information plus proliferation score plus tumour size**

Based on six reanalyses of RCTs and two retrospective analyses of prospective cohorts (total  $n = 9118$ ), Prosigna/ROR-PT was statistically significantly prognostic for unadjusted analyses of 10-year DRFS/DRFI in LN0 and LN+ patients. The 10-year DRFS/DRFI rates for low-risk patients were 95% to 97% in three studies of LN0 patients (endocrine monotherapy), and in LN+ patients these were 100% in two studies (endocrine monotherapy) and 92% in one study (all endocrine therapy and chemotherapy). For intermediate-risk patients, 10-year DRFS/DRFI rates were 87% to 93% for LN0 and 81% to 94% for LN+ (endocrine monotherapy). Prosigna/ROR-PT added prognostic information over clinicopathological variables or CTS/CLP/NPI in three studies; this was statistically significant in LN0 patients and either significant or borderline significant in LN+ patients.

### **EndoPredict and EndoPredict Clinical**

Based on three reanalyses of RCTs (total  $n = 3135$ ) in ER+ HER2– endocrine-treated patients, EPclin was statistically significantly prognostic for unadjusted analyses of 10-year DRFS/DRFI in LN0 and LN+ patients. The 10-year DRFS/DRFI rates for low-risk patients were approximately 95% in LN0 and LN+ patients receiving endocrine therapy only. EPclin added statistically significant information over CTS/NPI in LN0 and LN+ patients in TransATAC, while in two further studies, the EndoPredict score added statistically significant information over clinicopathological variables in mixed LN0/LN+ and LN+ patients (no data for EPclin).

### **IHC4**

The IHC4 has been validated in five reanalyses of RCTs and six retrospective cohort studies (total  $n = 13,434$ ) and provides statistically significant prognostic information consistently in unadjusted analyses in LN+/LN0, LN0 and LN+ groups. However, most studies used quartiles or tertiles to define risk groups, which are specific to each cohort and do not allow conclusions to be drawn about which cut-off points should be used in clinical practice and how these would perform. Many used laboratory methods that differed from the

derivation study methodology. Only one validation study<sup>126</sup> used the cut-off points from the original analysis,<sup>25</sup> and provides second and third validation cohorts (BCS and TEAM). IHC4 had additional prognostic value over clinicopathological factors in some studies. Test methodologies did not appear to have an impact on the statistical significance of results, but concerns remain about the conduct of the test in laboratories other than that used to derive the score.

### **IHC4+C**

The IHC4+C had prognostic value in one validation cohort (Nottingham) in which statistical significance was maintained after adjustments for clinicopathological factors.

### **Microarray studies**

Microarray studies are defined here as those that applied a test algorithm to either in silico data (microarray gene expression data held on a database) or a de novo microarray assessment. These studies support conclusions from studies using the commercial versions of the assays in suggesting that onco<sup>type</sup> DX, MammaPrint and EndoPredict can discriminate between high- and low-risk patients regardless of LN status.

## **Outcomes in low-risk and intermediate-risk groups**

### **Lymph node negative**

Among studies of LN0 patients receiving endocrine monotherapy, the 10-year DRFS/DRFI rates in low-risk groups were similar across all five tests (see *Table 57*): 93% to 97% for onco<sup>type</sup> DX (four studies<sup>46,49,50,52,60,61</sup>), 93% for MammaPrint (one study<sup>91</sup>), 95% to 97% for Prosigna/ROR-PT (three studies<sup>46,104,105,112</sup>), 94% for EPclin (one study<sup>46,118–120</sup>) and 96% for IHC4+C (one study<sup>46</sup>). Intermediate-risk groups for onco<sup>type</sup> DX, Prosigna/ROR-PT and IHC4+C had worse DRFS/DRFI rates than low-risk groups (EPclin and MammaPrint do not have intermediate-risk groups). Many studies of MammaPrint included some ER– patients, did not treat all patients with endocrine therapy, and treated some with chemotherapy; for these studies, 10-year DRFS/DRFI rates in low-risk groups were 80% to 90% (seven studies<sup>79,84,86,88,91,96</sup>).

### **Lymph node positive**

Among studies of LN+ patients receiving endocrine monotherapy (see *Table 57*), 10-year DRFS/DRFI rates in low-risk groups were less favourable for onco<sup>type</sup> DX (82%; one study<sup>46</sup>) than for Prosigna/ROR-PT (100%; two studies<sup>46,104,105</sup>), EPclin (95%; one study<sup>46,118–120</sup>) or IHC4+C (96%; one study<sup>46</sup>). There were no studies of MammaPrint in this population. Intermediate-risk patients had lower DRFS/DRFI than low-risk patients for onco<sup>type</sup> DX (75%, one study<sup>46</sup>), Prosigna/ROR-PT (81% to 94%, two studies<sup>46,104,105</sup>) and IHC4+C (75%, one study<sup>46</sup>). For MammaPrint, the only LN+ data were in populations that included some ER– patients, did not treat all patients with endocrine therapy, and treated some with chemotherapy; 10-year DRFS/DRFI rates in low-risk groups were 79% to 91% (two studies<sup>85,89</sup>).

## **Chemotherapy benefit**

Evidence of chemotherapy benefit was only assessed for onco<sup>type</sup> DX, onco<sup>type</sup> DX RSPC and MammaPrint. There was no chemotherapy benefit evidence for EndoPredict or EPclin, Prosigna/ROR-PT, IHC4 or IHC4+C.

### **Onco<sup>type</sup> DX and onco<sup>type</sup> DX RSPC**

Analyses were reported in five studies.<sup>50,53,61,64–67,70</sup> Two were reanalyses of RCTs (one LN0,<sup>50,61</sup> one LN+,<sup>53</sup> total  $n = 1018$ ) in which patients were randomised to endocrine monotherapy, or endocrine therapy plus chemotherapy. Three were observational studies<sup>64–67,70</sup> (total approximately 44,000 with some double-counting, two LN0,<sup>64,65,67,70</sup> one LN+/LN0<sup>66</sup>) in which patients were treated in accordance with usual practice and their onco<sup>type</sup> DX score. The two reanalyses of RCTs suggest that benefit from chemotherapy

is highest in *oncotype* DX high-risk patients. Unadjusted interaction tests between *oncotype* DX risk group and chemotherapy benefit were mainly statistically significant. Adjusted interaction tests were borderline significant in the NSABP-B20 cohort (significant in HER2– patients), whereas in SWOG-8814 they were significant when adjusted for some clinicopathological variables individually, but not when adjusting for ER determined by Allred status. However, part of the NSABP-B20 cohort was the derivation cohort for *oncotype* DX and this may bias results in favour of observing an interaction. The RSPC algorithm (*oncotype* DX plus age, tumour size and grade) showed a non-significant interaction test between chemotherapy benefit and RSPC risk group,<sup>44</sup> indicating that the incorporation of clinicopathological factors may reduce prediction of chemotherapy benefit, and therefore if chemotherapy decisions are based on an informal consideration of clinicopathological factors alongside the *oncotype* DX score, this may reduce the predictive ability of *oncotype* DX in clinical practice. Three observational cohort studies were at high risk of confounding; one reported a statistically significant interaction test adjusted for limited clinical factors. If predictive ability were assumed, it is unclear below which exact cut-off point patients could avoid chemotherapy (although one study suggests that this is a recurrence score of 20), as chemotherapy benefit is uncertain in the intermediate-risk group. Although the ongoing RCT TAILORx will address the issue of whether or not low-risk and intermediate-risk patients can avoid chemotherapy, it is unclear to what extent it will address the question of whether or not the test can predict chemotherapy benefit. The EAG considers that there remains uncertainty surrounding whether or not *oncotype* DX is associated with a predictive benefit of chemotherapy (i.e. a difference in relative effect by genomic risk group) and, if so, that there is uncertainty in the likely magnitude of this predictive effect within the clinical subgroups considered in this appraisal.

### **MammaPrint**

Prediction of chemotherapy benefit for MammaPrint was reported in a pooled analysis of six non-randomised series ( $n = 541$ ; half LN0, half LN1–3) in which patients were treated in accordance with usual practice. The effect of chemotherapy versus no chemotherapy was statistically significant in the MammaPrint high-risk group but not in the low-risk group in unadjusted analyses for 5-year DRFS and BCSS and in adjusted analyses for 5-year BCSS. However, the interaction test between chemotherapy treatment and risk group (for 5-year BCSS) was non-significant ( $p = 0.45$ ). A further pooled analysis of two of the above series, restricted to LN1–3 patients, also reported a statistically non-significant interaction between chemotherapy treatment and risk group for 10-year BCSS ( $p = 0.95$ ). The evidence for the ability of MammaPrint to predict chemotherapy benefit is therefore extremely limited; although unadjusted analyses suggest a greater effect of chemotherapy in high-risk groups, adjusted analyses were only reported for one outcome, and the non-significant interaction tests suggest no statistically significant difference in effect of chemotherapy between risk groups.

## **Clinical utility**

Clinical utility is defined in this assessment as the impact of tests used prospectively in clinical practice on recurrence/survival outcomes. Studies assessing prospective use of tests were only available for *oncotype* DX and MammaPrint, and only one RCT had reported in full (MINDACT for MammaPrint). There was no clinical utility evidence for EndoPredict or EPclin, Prosigna/ROR-PT, IHC4, IHC4+C or *oncotype* DX RSPC.

### **Oncotype DX**

Without the highest level of evidence (RCT of treatment guided by a test vs. treatment guided by usual practice), it is not possible to conclude whether or not patient outcomes would be affected by the use of the test in a clinical setting. In LN0 patients, the use of the test in clinical practice appears to result in low rates of chemotherapy use in low-risk patients (2% to 12%), with acceptable outcomes (5-year DRFS/DRFI/IDFS of 96% to 99.6%). Rates of chemotherapy use increased with increasing risk category, and were generally higher in LN+ patients; only one study reported 5-year DRFS/DRFI/IDFS for LN+ patients, which was 97% (7% received chemotherapy). It was not possible to determine whether or not patients in

intermediate- and high-risk categories had better outcomes than low-risk patients as a result of using onco $type$  DX, owing to the observational nature of the studies.

### MammaPrint

Two studies reported evidence relating to the clinical utility of MammaPrint. MINDACT is a RCT of MammaPrint versus clinical practice. This study randomised patients with discordant MammaPrint and mAOL risks to chemotherapy or no chemotherapy. For patients who were high-clinical, low-MammaPrint risk, 5-year DMFS was 95.9% with chemotherapy and 94.4% without chemotherapy, a non-significant absolute difference of 1.5% ( $p = 0.267$ ). This raises the possibility of avoiding chemotherapy in these patients. In patients who were low-clinical, high-MammaPrint risk, 5-year DMFS was 95.8% with chemotherapy and 95.0% without chemotherapy, an absolute difference of 0.8%. This could be interpreted as showing that MammaPrint may not be useful in this group as it would increase chemotherapy rates without improving outcomes. However, the comparator was mAOL, and it is unclear whether or not the same would be true for other clinical risk scores.

RASTER is a prospective observational study in which patients were treated in accordance with MammaPrint plus usual clinical practice (LN0) or in accordance with usual clinical practice (LN+). The 5-year DRFI for LN0 patients was 97.0% for low-risk patients (15% had chemotherapy) and 91.7% for high-risk patients (81% received chemotherapy). The 10-year DRFI for LN0 patients was 93.7% for low-risk patients and 86.8% for high-risk patients. The DRFI rates in the MammaPrint low-risk group may be considered sufficiently low for these patients to avoid chemotherapy.

### Decision impact

Decision impact studies assess how decisions to use or not to use chemotherapy change pre and post use of the test. Only decision impact studies from the UK and Europe were included, because other countries may have very different rates of chemotherapy use. The percentage of patients with any change in treatment recommendation or decision (either to or from chemotherapy) among UK studies was 29% to 49% across four onco $type$  DX studies, 37% in one EndoPredict study and 27% in one IHC4+C study. Ranges across European (non-UK) studies were 5% to 70% for onco $type$  DX, 38% to 41% for EndoPredict, 14% to 41% for Prosigna and 13% to 51% for MammaPrint. The net change in the percentage of patients with a chemotherapy recommendation or decision (patients changing to chemotherapy minus those changing to no chemotherapy) among UK studies was a reduction of 8% to 23% across four onco $type$  DX studies, an increase of 1% in one EndoPredict study and a reduction of between 2% and 26% in one IHC4+C study (unclear owing to category definitions). Net changes across European (non-UK) studies were a reduction of 0% to 64% for onco $type$  DX, a reduction of 13% to 26% for EndoPredict, a reduction of 2% to an increase of 9% for Prosigna and a reduction of 31% to an increase of 8% for MammaPrint.

### Concordance

Concordance is defined in this review as the degree to which tests assign the same patients to the same risk groups. Concordance analyses do not report long-term outcomes. A full review of these data was beyond the scope of this review and, instead, the OPTIMA Prelim study<sup>588</sup> was included as a key example of concordance between tests and included onco $type$  DX, MammaPrint, Prosigna and IHC4. The authors concluded, that although tests assigned similar proportions of patients to low/intermediate- and high-risk categories, test results for an individual patient could differ markedly depending on which test was used.

## Anxiety and health-related quality of life

Six studies (seven publications)<sup>159,164,166,174–177</sup> reported outcomes relating to anxiety (including worry and distress) and HRQoL. For *oncotype* DX (two studies,  $n = 286$ ),<sup>174,176</sup> *EndoPredict* (one study,  $n = 149$ )<sup>159</sup> and *Prosigna* (two studies,  $n = 398$ ),<sup>163,166</sup> all studies had a pre–post test design, whereas *MammaPrint* compared patients subgrouped in accordance with their clinical risk, *MammaPrint* risk, whether or not they were assigned to chemotherapy and whether or not the *MammaPrint* test result was missing.<sup>177</sup> Across tests, and when reported, state anxiety decreased post test and total FACT-G scores generally stayed the same. However, without a comparator group it is not possible to tell if anxiety would have reduced post treatment decision regardless of how the decision was made. Emotional and functional well-being in FACT-G improved in one study,<sup>166</sup> and FACT-B scores improved for some subgroups in one study.<sup>177</sup>

## Time-to-test results

One study<sup>181</sup> of 263 US patients reported that the percentage having a delay of  $\geq 42$  days from surgery to chemotherapy initiation was 31% for patients for whom an *oncotype* DX test was ordered, compared with 20% for other patients. In another study, the median handling time was 3 working days (range 0–11 days), and 59% of tests were conducted within 3 days.<sup>161</sup>

## Appendix 5 Results: all tests compared with each other

This appendix provides an overview of three types of studies that allow some form of comparison between tests:

1. Studies reporting more than one test – these are studies in which two or more of the tests were conducted and patient outcomes were reported, such that the prognostic performance of two or more tests in the same cohort can be compared. Very few studies conduct formal comparisons between tests.
2. Microarray studies – these are studies in which the commercial version of the tests was not conducted; rather, test algorithms were applied to genetic profiles obtained using microarray techniques. Mostly, these are publicly available in silico (electronic database) genetic profiles, complete with patient outcome data. As with the studies that report more than one test, the comparisons provided are not always formal.
3. Concordance in risk categorisation between tests – focusing on the OPTIMA Prelim study.

### Studies reporting more than one test

#### *Prognostic performance: studies assessing multiple tests*

Few studies assessed multiple tests in the same cohort. This section of the report focuses on how the tests compare with each other in terms of prognostic performance. Evidence is often limited and formal statistical comparisons are often lacking.

#### *Study designs: studies assessing multiple tests*

Data were reported for six cohorts (*Table 58*). Four studies were reanalyses of RCTs (TransATAC;<sup>46</sup> ABCSG 6 and ABCSG 8<sup>118–120</sup> and ABCSG 8 only;<sup>104,105</sup> GEICAM 9906;<sup>108,109</sup> and WSG PlanB<sup>73,74,77</sup>). The most comprehensive analysis in terms of the number of tests compared was the translational research analysis of UK-based patients from the ATAC<sup>589</sup> trial (TransATAC; see *Report Supplementary Material 1*), which assessed four tests: EndoPredict, Prosigna, oncotype DX and IHC4+C. Analyses were reported across 10 publications,<sup>25,36–44</sup> but none reported only ER+, HER2–, LNO–3 patients. In this section of the report, we use the reduced TransATAC data set (only including patients with a result for all four tests), whereas we have used the data from the full analysis set (where all patients with the relevant test were included) in the sections relating to each of the tests individually (see *Chapter 2*). A pooled analysis of 1702 patients from the ABCSG 6 and ABCSG 8 trials assessing EndoPredict (EndoPredict and EPclin) was reported by Dubsy *et al.*<sup>119,120</sup> plus subgroup analyses submitted to NICE by Myriad Genetics,<sup>117,118</sup> and an analysis of 1397 patients from ABCSG 8 only assessed Prosigna (Gnant *et al.*<sup>104</sup> and Filipits *et al.*<sup>105</sup>). Because these two analyses have a large overlap (the majority of patients are from ABCSG 8), they are used here to compare EndoPredict and Prosigna. Finally, 555 patients from the Spanish GEICAM 9906 trial were analysed for EndoPredict (EndoPredict and EPclin) and Prosigna by Martin *et al.*<sup>108,109</sup> WSG PlanB<sup>73,74,77</sup> was a reanalysis of RCT data from Germany, but has limitations in its use for assessing prognostic performance (discussed in the next paragraph).

The three remaining studies (Russell *et al.*,<sup>57</sup> WSG PlanB<sup>73,74,77</sup> and Gong *et al.*,<sup>58</sup> see *Table 58*) all had limitations. Russell *et al.*<sup>57</sup> was an observational study of oncotype DX and MammaPrint in which patients were treated in accordance with MammaPrint results, and is therefore confounded as a prognostic study as chemotherapy treatment is likely to have differed across risk groups. However, as there were no other data that compared MammaPrint with other tests, except from microarray studies (see *Appendix 5* and *Report Supplementary Material 10*), it has been included as the next available level of evidence. Two studies (WSG PlanB<sup>73,74,77</sup> and Gong *et al.*<sup>58</sup>) that both have limitations were included because they compared oncotype DX with IHC4, and the only other data (apart from microarray studies) that compare oncotype DX with IHC4 are from the IHC4 derivation cohort (TransATAC). WSG PlanB<sup>73,74,77</sup> was a reanalysis of RCT data from Germany and was included as a clinical utility study for oncotype DX (see *Chapter 2*,

**TABLE 58** Characteristics of prognostic studies: multiple tests

Study (first author and year)	Cohort(s)	Number of patients	Country	Study design	Test	Details of test	Cut-off points	Population	Nodal status	ET/chemotherapy
Sestak 2017 (data requested) <sup>146</sup>	TransATAC	774	UK	R-RCT	EPclin	FFPE	3.3	ER+ HER2–	LN0, 76%	ET 5 years
						RT-qPCR		Postmenopausal	LN1–3, 24%	No chemotherapy
					OncoType DX	FFPE	18–30	100% female		
						Genomic Health				
					OncoType DX RSPC	FFPE	10 year DR risk < 10%, 10–20%, > 20%			
	Genomic Health									
	Prosigna	FFPE	LN0: 41–60							
		NanoString Technologies nCounter	LN+: 16–40							
	IHC4+C	FFPE	10–20							
		Cuzick <i>et al.</i> 2011 <sup>25</sup>								
Dubsky 2013, <sup>119,120</sup> Myriad Genetics <sup>118</sup>	ABCSG 6 and ABCSG 8	1702 (all)	Austria	R-RCT	EndoPredict	FFPE	5	ER+ HER2–	LN0, 68%	ET 5 years
					EPclin	RT-qPCR	3.3	Postmenopausal	LN1–3, 27%	No chemotherapy
								Stage I–II	LN > 3, 5%	
								100% female		
Gnant 2014, <sup>104</sup> Filipits 2014 <sup>105</sup>	ABCSG 8	1397			Prosigna	FFPE	LN0: 40–60	ER+ HER2–	LN0, 71% <sup>a</sup>	
						nCounter	LN1–3: 15–40	Postmenopausal	LN1–3, 26% <sup>a</sup>	
							LN > 3: all high	100% female	LN > 3, 3% <sup>a</sup>	
Martin 2016, <sup>108</sup> Martin 2014 <sup>109</sup>	GEICAM 9906	555	Spain	R-RCT	EndoPredict	FFPE	5	ER+ HER2–	All LN+	Adjuvant chemotherapy (FEC/FEC-P)
					EPclin	RT-qPCR	3.3	46% postmenopausal	LN1–3, 64%	
					Prosigna	RT-qPCR, then microarray	18–65	Stage II–III	LN > 3, 36%	ET 5 years
								100% female		

Study (first author and year)	Cohort(s)	Number of patients	Country	Study design	Test	Details of test	Cut-off points	Population	Nodal status	ET/chemotherapy
Russell 2016 <sup>57</sup>	University of South Florida; Morton Plan Hospital	135	USA	Observational, RPWT	OncoType DX MammaPrint	NR NR	NR	100% ER+ HER2- NR Menopausal NR Female NR	NR	NR – RPWT
Nitz 2017, <sup>77</sup> Gluz 2016 <sup>73,74</sup>	WSG PlanB	2642	Germany	R-RCT	OncoType DX IHC4	NR Genomic Health PE IHC4 Prat <i>et al.</i> 2013 <sup>590</sup> Cuzick <i>et al.</i> 2011 <sup>25</sup>	25th–75th percentile 25th–75th percentile	HR+ HER2- Premenopausal/ postmenopausal 100% female High clinical risk <sup>b</sup>	LN0–3 LN0 58.8% LN1–3 41.2%	RS < 12, ET monotherapy; RS ≥ 12, chemotherapy plus ET <sup>c</sup>
Gong 2016 <sup>58</sup>	SYSMH; CCSYU; 3rd HNC	153	China	Observational, RPWOT	OncoType DX IHC4	FFPE Multiplex branched-DNA liquid chip technology (SurExam, Guangzhou, China) IHC4 Cuzick <i>et al.</i> 2011 <sup>25</sup>	NR 25th–75th percentile	100% HR+ 100% HER2- 61% postmenopausal % female NR Non-metastatic	LN0	100% ET 79% chemotherapy

3rd HNC, Third Hospital of Nanchang City; ET, endocrine therapy; FEC, 5-fluorouracil, epirubicin and cyclophosphamide; FEC-P, FEC + paclitaxel; N+, node positive; N0, node negative; R-RCT, reanalysis of RCT; RPWT, routine practice with MammaPrint test results; RS, recurrence score; SYSMH, Sun Yat-sen Memorial Hospital.

a Nodal status for all 1478 patients; NR for 1397 who were HER2-.

b HER2- negativity; pT1–T4c; LN+ [or LN0 with a risk factor (CpT2, grade 2/3, high uPAVPAI-1, < 35 years or HR-negative)].

c Patients were treated in accordance with oncoType DX score, with those with RS < 12 receiving ET only, and those with RS ≥ 12 receiving chemotherapy plus ET.

*Clinical utility: oncotype DX*) as patients were not treated with chemotherapy when the recurrence score was < 12, and as a prognostic study for IHC4 (see Section 2.7.2). Gong *et al.*<sup>58</sup> is an observational study in which patients were treated in accordance with usual practice and it was not clear if this included the test result, and the assay used was not the commercial version of oncotype DX.

As the TransATAC analysis is key to this assessment and compares the most in-scope tests ( $n = 4$ ), to simplify the write-up we have structured this section of the report around the TransATAC data and compared other data with these, or used other data to provide comparative data when TransATAC data are lacking. The section contents are:

- TransATAC<sup>46</sup> comparing oncotype DX, EPclin, Prosigna and IHC4+C.
- EndoPredict compared with EPclin ( $n = 2$  studies, ABCSG 6 plus ABCSG 8; and GEICAM 9906).<sup>108,109,118–120</sup>
- EPclin compared with Prosigna ( $n = 3$  studies, TransATAC; GEICAM 9906; ABCSG 6 plus ABCSG 8 or ABCSG 8).<sup>42,104,105,108,109,118–120</sup>
- Oncotype DX compared with MammaPrint ( $n = 1$  study<sup>57</sup>). The limitations of Russell *et al.*<sup>57</sup> are discussed in the following section.
- Oncotype DX compared with IHC4 or IHC4+C ( $n = 3$  studies<sup>46,58,73,74,77</sup>). The limitations of WSG PlanB<sup>73,74,77</sup> and Gong *et al.*<sup>58</sup> are discussed in the following section.

### **Patients and treatments: studies assessing multiple tests**

Patient characteristics and details of the treatments received are presented in *Table 58*. Six of the seven data sets consisted of, or had analyses available for, ER+, HER2– patients,<sup>46,58,73,74,77,104,105,108,109,118–120</sup> whereas Russell *et al.*<sup>57</sup> consisted of all ER+ patients, but did not report the proportion who were HER2–.<sup>57</sup> In terms of nodal status, one study was in LNO patients only,<sup>58</sup> one study was in LN+ patients only<sup>108,109</sup> and one did not report nodal status.<sup>57</sup> Three data sets included node-negative and node-positive patients (TransATAC, ABCSG 6 plus ABCSG 8 and WSG PlanB<sup>104,105,118–120</sup>). In GEICAM 9906,<sup>108,109</sup> 36% of participants had more than three positive nodes; in ABCSG 6 plus ABCSG 8,<sup>118–120</sup> 5% had more than three positive nodes. In WSG PlanB, patients were at clinically high risk, defined as LN+ or LNO with a risk factor (CpT2, grade 2/3, high uPA/PAI-1, < 35 years).<sup>73,74,77</sup> Patients in all analyses received 5 years of endocrine therapy, apart from those in the study by Russell *et al.*,<sup>57</sup> in which this was not reported, and Gong *et al.*,<sup>58</sup> in which 100% of participants received endocrine therapy, but the duration was not reported. Patients in the GEICAM 9906 analysis<sup>108,109</sup> also received adjuvant chemotherapy; Russell *et al.*<sup>57</sup> did not report how many patients received chemotherapy; WSG PlanB<sup>73,74,77</sup> patients with a recurrence score of  $\geq 12$  received chemotherapy; and 79% of patients in Gong *et al.*<sup>58</sup> received chemotherapy.

### **Tests and comparators: studies assessing multiple tests**

Details of the tests conducted and the cut-off points applied are presented in *Table 58*. All data sets that included EndoPredict and Prosigna assessed EndoPredict as marketed, using RT-qPCR and standard cut-off points for risk groups (5 for EndoPredict and 3.3 for EPclin). In two analyses (TransATAC and ABCSG 6 plus ABCSG 8<sup>104,105</sup>), Prosigna was assessed using the nCounter device and cut-off points of 40 and 60 (LNO) or 15 and 40 (LN1–3), while GEICAM 9906<sup>108,109</sup> used a ‘research-based non-standardised’ PAM50 ROR-PT assay, using RT-qPCR then microarray rather than nCounter, with cut-off points of 18 and 65 (LN+). Russell *et al.*<sup>57</sup> did not report how oncotype DX and MammaPrint were obtained. WSG PlanB<sup>73,74,77</sup> ordered oncotype DX from Genomic Health and conducted IHC4 tests according to Prat *et al.*<sup>590</sup> and Cuzick *et al.*,<sup>25</sup> and used 25th to 75th percentiles as cut-off points for oncotype DX and IHC4. Gong *et al.*<sup>58</sup> conducted oncotype DX assays using SurExam (Guangzhou, China) and IHC4 according to Cuzick *et al.*,<sup>25</sup> also using 25th to 75th percentiles as cut-off points.

Comparators in TransATAC<sup>39,46</sup> included the CTS score and NPI. ABCSG 6 plus ABCSG 8<sup>118–120</sup> compared AOL with EndoPredict.

### **Quality assessment: studies assessing multiple tests**

A summary of the quality of the studies is presented in *Table 59*. Two data sets (TransATAC and ABCSG 8 or 6 + 8)<sup>41,46,104,105,118–120</sup> were reanalyses of RCTs in which no patients received chemotherapy and all

**TABLE 59** Quality assessment of prognostic studies: multiple tests

Study (first author and year)	Cohort(s)	Derivation or validation?	Study design appropriate?	All eligible patients included?	Blinding (of test assessors to outcomes)?	Outcome definition standardised or a priori?	Applicability: patient spectrum	Applicability: test as per decision problem?
Sestak 2017 (data request) <sup>46</sup>	TransATAC	V	Yes, R-RCT, no chemotherapy	No; InT, FT	Yes	Yes	Yes	Yes
Dubsky 2013, <sup>119,120</sup> Myriad Genetics <sup>118</sup>	ABCSG 6 plus ABCSG 8	V	Yes, R-RCT, no chemotherapy	UC	UC	Yes	N, includes 5% LN > 3	Yes
Gnant 2014, <sup>104</sup> Filipits 2014 <sup>105</sup>	ABCSG 8	V	Yes, R-RCT, no chemotherapy	No; InT, MS, TF	Yes	Yes	Yes (for subgroup analysis)	Yes
Martin 2016, <sup>108</sup> 2014 <sup>109</sup>	GEICAM 9906	V	No, R-RCT, adjuvant chemotherapy	No (reason NR)	Yes	Yes	N (36% LN > 3)	No, Prosigna via RT-qPCR then microarray
Nitz 2017, <sup>77</sup> Gluz 2016, <sup>73,74</sup>	WSG PlanB	V	No, some chemotherapy	No, MS	Yes	Yes	Yes, but high risk	Yes
Russell 2016 <sup>57</sup>	University of South Florida; Morton Plan Hospital	V	No, cohort study, usual practice (some chemotherapy)	No; InT, sent for test	UC	Yes	N; InT	Yes
Gong 2016 <sup>58</sup> (n = 611)	SYSMH; CCSYU; 3rd HNC	V	No, some chemotherapy	No; InT; MD	UC	Yes	N, InT, MD, chemotherapy	No – oncotype DX algorithm, but used SurExam assay

3rd HNC, Third Hospital of Nanchang City; D, Development; FT, failed test; InT, insufficient tissue; MS, missing samples; N, number of positive nodes; R-RCT, reanalysis of RCT; SYSMH, Sun Yat-sen Memorial Hospital; TF, test failure; UC, unclear; V, validation.

received adjuvant endocrine therapy. Two (GEICAM and WSG PlanB)<sup>73,74,77,108,109</sup> were reanalyses of RCTs in which some patients received chemotherapy, and two<sup>57,58</sup> were observational studies in which patients were either treated in accordance with routine practice but it was not clear if the test results were known,<sup>58</sup> or were treated in accordance with routine practice including a test result (MammaPrint).<sup>57</sup> None of the studies reported including all relevant patients, meaning that there is a risk of bias and the generalisability of the cohort to the decision problem is uncertain. Test assessors were blind to patient outcomes in four studies.<sup>46,73,74,77,104,105,108,109</sup> All used standardised outcomes. Two studies<sup>58,108,109</sup> used assays that were not the same as the commercially marketed version of the test: Prosigna not using nCounter in one study,<sup>108,109</sup> oncotype DX performed by SurExam and the IHC4 process was not clear in one study.<sup>58</sup>

### Results: studies assessing multiple tests

Tables 60–63 present the data for all patients (node positive or node negative) and separate data for node-positive and node-negative patients.

### Prognostic performance

#### Distribution of patients by risk group, event rates (distant recurrence/relapse-free interval/distant metastasis-free survival/distant recurrence/relapse-free survival) and hazard ratios (unadjusted analyses)

This section reports unadjusted analyses. Adjusted analyses, which show whether or not the test has prognostic value over clinicopathological variables, are reported in *Additional prognostic value*.

#### TransATAC data

In the TransATAC cohort (see Table 60),<sup>42,46</sup> the proportion of patients categorised as low risk was similar for oncotype DX, EPclin and IHC4+C (62%, 61% and 57%, respectively), and Prosigna placed the fewest patients in this group (43%). In the LN0 subgroup, the proportion in the low-risk group was generally higher (63% for oncotype DX, 73% for EPclin, 66% for IHC4+C, 54% for Prosigna and 73% for oncotype DX RSPC) than in the LN+ group (57%, 23%, 27% and 8%, respectively; oncotype DX RSPC not assessed in LN+). Notably, oncotype DX categorised a high proportion as low risk in both subgroups (63% and 57%, respectively), and Prosigna always reported the smallest proportion (54% and 8%, respectively). The 5-year event rates in low-risk LN0 patients were largely similar across tests, ranging from 97.6% (EPclin) to 98.8% (oncotype DX), but at 10 years Prosigna low-risk patients had the best DRFI rates (97.0%) with the other four tests having similar rates (93.4% to 94.7%). In LN+ patients, event rates in low-risk patients were more variable, with DRFI rates ranging from 95.1% (oncotype DX) to 100% (Prosigna) at 5 years, and 80.6% (oncotype DX) to 100% (Prosigna) at 10 years. Notably, oncotype DX consistently had the worst survival rates in low-risk patients at both time points, whereas Prosigna had the best. However, only 8% of patients were assigned low-risk status by Prosigna, whereas 57% were assigned low-risk status by oncotype DX. IHC4+C and EPclin assigned fewer patients (27% and 23%, respectively) to the low-risk group than oncotype DX, but more than Prosigna, and had event rates of 95.2% and 94.4%, respectively.<sup>46</sup>

In LN0–3 patients, the HRs for 10-year DRFI between risk groups were all statistically significant, with HRs for low vs. high risk ranging from 4.41 (oncotype DX) to 12.40 (Prosigna). In LN0 patients, there was not a consistent pattern regarding whether HRs were greater at 0–5 years than at 0–10 years. All were statistically significant except the analysis comparing low- with high-risk patients for Prosigna at 5 years [2.91 (95% CI 0.95 to 8.89)]. The greatest HR was for the analysis of low- versus high-risk patients for oncotype DX [13.07 (95% CI 3.93 to 43.41)], and the lowest was for Prosigna at 5 years [2.91 (95% CI 0.95 to 8.89)]. When comparing LN0 with LN+ HRs, both EPclin and IHC4+C tests reported lower HRs in the LN0 subgroup than in the LN+ subgroup at 10 years, whereas oncotype DX reported higher HRs in the LN0 subgroup than in the LN+ subgroup.<sup>46</sup>

TABLE 60 Prognostic performance of multiple tests: DRFI/DMFS/DRFS<sup>a</sup>

Study (first author and year)	Cohort(s), design, country	Population	Nodal status	ET/chemotherapy	Test	Percentage of patients per group			Percentage risk								
						Low	Intermediate	High	0–5 years			0–10 years			DRFI/DMFS/DRFS: <sup>a</sup> HR (95% CI)		
<b>Node negative and node positive</b>																	
Sestak 2017 (data request) <sup>46</sup> (reduced data set) <sup>b</sup>	TransATAC, R-RCT, UK	ER+ HER2–, (n = 774)	<ul style="list-style-type: none"> <li>LN0, 76%</li> <li>LN1–3, 24%</li> </ul>	<ul style="list-style-type: none"> <li>All ET</li> <li>No chemotherapy</li> </ul>	EPclin	61	–	39	–	–	–	–	–	–	–	0–10 years: 4.65 (2.98 to 7.24)	
					Oncotype DX	62	28	10	–	–	–	–	–	–	–	–	0–10 years: <ul style="list-style-type: none"> <li>Low vs. intermediate: 2.72 (1.74 to 4.27)</li> <li>Low vs. high: 4.41 (2.60 to 7.51)</li> </ul>
					Prosigna	43	30.5	26.5	–	–	–	–	–	–	–	–	0–10 years: <ul style="list-style-type: none"> <li>Low vs. intermediate: 5.49 (2.63 to 11.48)</li> <li>Low vs. high: 12.40 (6.13 to 25.08)</li> </ul>
					IHC4+C	57	26	17	–	–	–	–	–	–	–	–	0–10 years: <ul style="list-style-type: none"> <li>Low vs. intermediate: 4.73 (2.79 to 8.03)</li> <li>Low vs. high: 7.18 (4.20 to 12.28)</li> </ul>
Dubsky 2013, <sup>119,120</sup> Myriad Genetics <sup>118</sup>	ABCSG 6 plus ABCSG 8, R-RCT, Austria	ER+ HER2–, (n = 1702)	<ul style="list-style-type: none"> <li>LN0, 68%</li> <li>LN1–3, 27%</li> <li>LN &gt; 3, 5%</li> </ul>	<ul style="list-style-type: none"> <li>All ET</li> <li>No chemotherapy</li> </ul>	EndoPredict	49	–	51	–	–	–	NR	–	NR	0–5 years: 2.80 (1.81 to 4.34); p < 0.001		
					EPclin	63	–	37	–	–	–	95.3	–	NR	0–5 years: 4.82 (3.12 to 7.44); p < 0.001		
Gnant 2014, <sup>104</sup> Filipits 2014 <sup>105</sup>	ABCSG 8, R-RCT, Spain	ER+ HER2–, (n = 1397)	<ul style="list-style-type: none"> <li>LN0, 71%<sup>c</sup></li> <li>LN1–3, 26%<sup>c</sup></li> <li>LN &gt; 3, 3%<sup>c</sup></li> </ul>	<ul style="list-style-type: none"> <li>All ET</li> <li>No chemotherapy</li> </ul>	Prosigna	35	32	33	–	–	–	96.6	91.1	79.9	5–15 years: <ul style="list-style-type: none"> <li>Intermediate vs. low: 3.74 (NR); p = 0.002<sup>f</sup></li> <li>High vs. low: 6.90 (3.08 to 15.45); p &lt; 0.001<sup>f</sup></li> </ul>		

continued

TABLE 60 Prognostic performance of multiple tests: DRFI/DMFS/DRFS<sup>a</sup> (continued)

Study (first author and year)	Cohort(s), design, country	Population	Nodal status	ET/chemotherapy	Test	Percentage of patients per group		Percentage risk						DRFI/DMFS/DRFS: <sup>a</sup> HR (95% CI)	
						Low	Intermediate	High	0–5 years			0–10 years			
Nitz 2017, <sup>77</sup> Gluz 2016 <sup>73,74</sup>	WSG PlanB, Germany	HR+ HER2–, (n = 2642)	<ul style="list-style-type: none"> <li>LN0–3</li> <li>LN0 58.8%</li> <li>LN1–3 41.2%</li> </ul>	RS < 12 ET; RS ≥ 12, chemotherapy and ET <sup>d</sup>	Oncotype DX	17 <sup>e</sup>	58 <sup>e</sup>	21 <sup>e</sup>	93.6 <sup>d</sup>	94.3 <sup>d</sup>	84.2 <sup>d</sup>				0–5 years: 2.33 (1.73 to 3.14); p < 0.001
					IHC4	NR	NR	NR	NR	NR	NR				0–5 years: 2.04 (1.47 to 2.83); p < 0.001
Russell 2016 <sup>57</sup>	University of South Florida, Morton Plan Hospital, USA	ER+, NR HER2–, (n = 135)	NR	NR	Oncotype DX	53	26	21							Log-rank 0–5 years:  <ul style="list-style-type: none"> <li>Intermediate vs. low: p = 0.760</li> <li>High vs. low: p = 0.036</li> </ul>
					MammaPrint	63		72							Log-rank, 0–5 years: p = 0.032
<b>Node negative</b>															
Sestak 2017 (data request) <sup>46</sup> (reduced data set) <sup>b</sup>	TransATAC, R-RCT, UK	ER+ HER2–, (n = 591)	LN0	<ul style="list-style-type: none"> <li>All ET</li> <li>No chemotherapy</li> </ul>	EPclin	73	–	27	97.6	–	91.2	93.4	–	77.9	0–5 years: 3.76 (1.67 to 8.46)  0–10 years: 3.88 (2.31 to 6.52)
					Oncotype DX	63	26	10	98.8	92.1	86.8	94.1	83.3	72.8	0–5 years:  <ul style="list-style-type: none"> <li>Low vs. intermediate: 7.40 (2.39 to 22.93)</li> <li>Low vs. high: 13.07 (3.93 to 43.41)</li> </ul> 0–10 years:  <ul style="list-style-type: none"> <li>Low vs. intermediate: 3.28 (1.79 to 5.98)</li> <li>Low vs. high: 5.83 (2.96 to 11.48)</li> </ul>
					Oncotype DX RSPC	73	19	9	98.3	91.4	86.2	93.8	80.2	70.5	0–5 years:  <ul style="list-style-type: none"> <li>Low vs. intermediate: 5.42 (1.88 to 15.63)</li> <li>Low vs. high: 8.74 (2.82 to 27.11)</li> </ul> 0–10 years:  <ul style="list-style-type: none"> <li>Low vs. intermediate: 3.67 (1.92 to 7.01)</li> <li>Low vs. high: 6.07 (2.96 to 14.43)</li> </ul>

Study (first author and year)	Cohort(s), design, country	Population	Nodal status	ET/chemotherapy	Test	Percentage risk									DRFI/DMFS/DRFS: <sup>a</sup> HR (95% CI)
						Percentage of patients per group			0–5 years			0–10 years			
						Low	Intermediate	High	Low	Intermediate	High	Low	Intermediate	High	
					Prosigna	54	30	16	98.4	95.4	88.1	97.0	85.9	67.6	0–5 years: <ul style="list-style-type: none"> <li>Low vs. intermediate: 2.91 (0.95 to 8.89)</li> <li>Low vs. high: 7.62 (2.65 to 21.92)</li> </ul> 0–10 years: <ul style="list-style-type: none"> <li>Low vs. intermediate: 4.60 (2.12 to 9.99)</li> <li>Low vs. high: 12.19 (5.73 to 25.95)</li> </ul>
					IHC4+C	66	23	11	98.4	93.2	85.7	94.7	79.8	74.6	0–5 years: <ul style="list-style-type: none"> <li>Low vs. intermediate: 4.51 (1.60 to 12.66)</li> <li>Low vs. high: 9.78 (3.48 to 27.49)</li> </ul> 0–10 years: <ul style="list-style-type: none"> <li>Low vs. intermediate: 3.98 (2.18 to 7.28)</li> <li>Low vs. high: 6.06 (3.07 to 11.94)</li> </ul>
Gnant 2014, <sup>104</sup> Filipits 2014 <sup>105</sup>	ABCSG 8, R-RCT, Austria	ER+ HER2–, (n = 984)	LN0	<ul style="list-style-type: none"> <li>All ET</li> <li>No chemotherapy</li> </ul>	Prosigna	48	32	20				96.5	90.0	84.7	5–15 years: <ul style="list-style-type: none"> <li>Intermediate vs. low: 4.03 (NR); <math>p = 0.002^f</math></li> <li>High vs. low: 4.74 (1.89 to 11.87); <math>p &lt; 0.001^f</math></li> </ul>
Gong 2016 <sup>58</sup>	SYSMH, CCSYU, 3rd HNC, China	ER+ HER2–, (n = 153)	LN0	<ul style="list-style-type: none"> <li>100% ET</li> <li>79% chemotherapy</li> </ul>	Oncotype DX	49	26	25							0–10 years C-index (AUC): 0.685 (0.540 to 0.830)
					IHC4	29	48	23							0–10 years C-index (AUC): 0.602 (0.436 to 0.767)

continued

**TABLE 60** Prognostic performance of multiple tests: DRFI/DMFS/DRFS<sup>a</sup> (continued)

Study (first author and year)	Cohort(s), design, country	Population	Nodal status	ET/chemotherapy	Test	Percentage of patients per group			Percentage risk						DRFI/DMFS/DRFS: <sup>a</sup> HR (95% CI)	
						Low	Intermediate	High	0–5 years			0–10 years				
<b>Node positive</b>																
Sestak 2017 (data request) <sup>46</sup> (reduced data set) <sup>b</sup>	TransATAC, R-RCT, UK	ER+ HER2–, (n = 183)	LN1–3	<ul style="list-style-type: none"> <li>All ET</li> <li>No chemotherapy</li> </ul>	EPclin	23	–	77	97.7	–	86.7	94.4	–	69.7	0–5 years: 5.89 (0.79 to 44.15)	
															0–10 years: 6.58 (1.59 to 27.27)	
					Oncotype DX	57	32	11	95.1	82.0	79.7	80.6	70.9	62.0	0–5 years:	
																<ul style="list-style-type: none"> <li>Low vs. intermediate: 3.83 (1.31 to 11.20)</li> <li>Low vs. high: 4.69 (1.26 to 17.47)</li> </ul>
																0–10 years:
																<ul style="list-style-type: none"> <li>Low vs. intermediate: 1.89 (0.96 to 3.74)</li> <li>Low vs. high: 2.77 (1.15 to 6.68)</li> </ul>
					Prosigna	8	32	60	100.0	91.1	86.8	100.0	79.3	69.3	0–5 years:	
															<ul style="list-style-type: none"> <li>Low vs. intermediate or low vs. high: no events</li> <li>Intermediate vs. high: 1.59 (0.57 to 4.41)</li> </ul>	
															0–10 years:	
															<ul style="list-style-type: none"> <li>Low vs. intermediate or low vs. high: no events</li> <li>Intermediate vs. high: 1.59 (0.80 to 3.19)</li> </ul>	
					IHC4+C	27	34	39	98.0	88.5	83.8	95.2	71.6	64.3	0–5 years:	
															<ul style="list-style-type: none"> <li>Low vs. intermediate: 5.88 (0.73 to 47.81)</li> <li>Low vs. high: 8.57 (1.11 to 66.41)</li> </ul>	
															0–10 years:	
															<ul style="list-style-type: none"> <li>Low vs. intermediate: 7.31 (1.68 to 31.78)</li> <li>Low vs. high: 9.57 (2.25 to 40.71)</li> </ul>	

Study (first author and year)	Cohort(s), design, country	Population	Nodal status	ET/chemotherapy	Test	Percentage of patients per group			Percentage risk						
						Low	Intermediate	High	0–5 years			0–10 years			DRFI/DMFS/DRFS: <sup>a</sup> HR (95% CI)
Gnant 2014, <sup>104</sup> Filipits 2014 <sup>105</sup>	ABCSG 8, R-RCT, Austria	ER+ HER2–, (n = 413)	<ul style="list-style-type: none"> <li>LN1–3, 89%<sup>c</sup></li> <li>LN &gt; 3, 11%<sup>c</sup></li> </ul>	<ul style="list-style-type: none"> <li>All ET</li> <li>No chemotherapy</li> </ul>	Prosigna	4	34	62				100	93.6	76.2	
Martin 2016, <sup>108</sup> 2014 <sup>109</sup>	GEICAM 9906, R-RCT, Spain	ER+ HER2–, (n = 536)	<ul style="list-style-type: none"> <li>LN1–3, 64%</li> <li>LN &gt; 3, 36%</li> </ul>	<ul style="list-style-type: none"> <li>All ET</li> <li>All chemotherapy</li> </ul>	EndoPredict	25	–	75				93	–	69	0–10 years: 4.7 (CI NR), <i>p</i> < 0.0001
					EPclin	13	–	87				100	–	71	0–10 years: not estimable; <i>p</i> < 0.0001
					ROR-PT (research)	19	56%	26				92	74	66	0–10 years: <ul style="list-style-type: none"> <li>4.4 (low vs. intermediate)</li> <li>5.8 (low vs. high) (CI NR); <i>p</i> &lt; 0.0001</li> </ul>

ET, endocrine therapy; N+, node positive; N0, node negative; NR, not reported; RS, recurrence score.

a DMFS (GEICAM, ABCSG); DRFI (TransATAC); DFS (Nitz *et al.*<sup>72</sup>).

b Full data set = all patients with EndoPredict data available; reduced data set = patients with data for all four in-scope tests analysed in TransATAC.

c Nodal status for all patients; NR for HER2– subgroup.

d Patients treated in accordance with RS: RS < 12 no chemotherapy, RS ≥ 12 chemotherapy.

e For cut-off points of < 12, 12–25 and > 25.

f 5–15 years in ABCSG-8 analysis of Prosigna.

TABLE 61 Prognostic performance of multiple tests: OS

Study (first author and year)	Cohort(s), design, country	Population	Nodal status	ET/chemotherapy	Test	Percentage of patients per group			OS at 5 years			OS at 10 years			HR, low vs. high (95% CI)
						Low	Intermediate	High	Low	Intermediate	High	Low	Intermediate	High	
<b>Node negative and node positive</b>															
Sestak 2017 <sup>46</sup> (reduced data set) <sup>a</sup>	TransATAC, R-RCT, UK	ER+ HER2-, (n = 774)	LN0, 76%	<ul style="list-style-type: none"> <li>All ET</li> <li>No chemotherapy</li> </ul>	EPclin	61	–	39	–	–	–	–	–	–	0–10 years: 2.15 (1.65 to 2.80)
			LN1–3, 24%		Oncotype DX	62	28	10	–	–	–	–	–	0–10 years: <ul style="list-style-type: none"> <li>Low vs. intermediate: 1.68 (1.25 to 2.26)</li> <li>Low vs. high: 2.59 (1.79 to 3.74)</li> </ul>	
					Prosigna	43	30.5	26.5	–	–	–	–	–	0–10 years: <ul style="list-style-type: none"> <li>Low vs. intermediate: 1.84 (1.29 to 2.61).</li> <li>Low vs. high: 3.42 (2.46 to 4.75)</li> </ul>	
					IHC4+C	57	26	17	–	–	–	–	–	0–10 years: <ul style="list-style-type: none"> <li>Low vs. intermediate: 2.19 (1.60 to 2.99)</li> <li>Low vs. high: 3.05 (2.20 to 4.22)</li> </ul>	
<b>Node negative</b>															
Sestak 2017 <sup>46</sup> (reduced data set) <sup>a</sup>	TransATAC, R-RCT, UK	ER+ HER2-, (n = 591)	LN0	<ul style="list-style-type: none"> <li>All ET</li> <li>No chemotherapy</li> </ul>	EPclin	73	–	27	92.8	–	88.9	79.6	–	63.3	0–5 years: 1.56 (0.87 to 2.79)
					Oncotype DX	63	26	10	94.4	87.7	85.2	80.7	69.2	55.8	0–5 years: <ul style="list-style-type: none"> <li>Low vs. intermediate: 2.24 (1.20 to 4.16)</li> <li>Low vs. high: 2.81 (1.28 to 6.13)</li> </ul> 0–10 years: <ul style="list-style-type: none"> <li>Low vs. intermediate: 1.75 (1.20 to 2.56)</li> <li>Low vs. high: 2.79 (1.76 to 4.42)</li> </ul>

Study (first author and year)	Cohort(s), design, country	Population	Nodal status	ET/chemotherapy	Test	Percentage of patients per group			OS at 5 years			OS at 10 years			HR, low vs. high (95% CI)
						Low	Intermediate	High	Low	Intermediate	High	Low	Intermediate	High	
					Oncotype DX RSPC	73	19	9	94.5	87.3	84.1	80.7	69.4	50.5	0–5 years: <ul style="list-style-type: none"> <li>Low vs. intermediate: 2.44 (1.19 to 4.99)</li> <li>Low vs. high: 3.08 (1.30 to 7.28)</li> </ul> 0–10 years: <ul style="list-style-type: none"> <li>Low vs. intermediate: 1.87 (1.22 to 2.96)</li> <li>Low vs. high: 3.33 (2.03 to 5.45)</li> </ul>
					Prosigna	54	30	16	93.4	92.7	84.1	83.6	72.7	51.7	0–5 years: <ul style="list-style-type: none"> <li>Low vs. intermediate: 1.12 (0.56 to 2.24)</li> <li>Low vs. high: 2.48 (1.28 to 4.82)</li> </ul> 0–10 years: <ul style="list-style-type: none"> <li>Low vs. intermediate: 1.75 (1.17 to 2.62)</li> <li>Low vs. high: 3.64 (2.41 to 5.48)</li> </ul>
					IHC4+C	66	23	11	94.9	85.3	85.7	82.2	63.1	57.3	0–5 years: <ul style="list-style-type: none"> <li>Low vs. intermediate: 3.00 (1.62 to 5.58)</li> <li>Low vs. high: 2.94 (1.34 to 6.47)</li> </ul> 0–10 years: <ul style="list-style-type: none"> <li>Low vs. intermediate: 2.31 (1.59 to 3.37)</li> <li>Low vs. high: 3.01 (1.90 to 4.78)</li> </ul>

continued



Study (first author and year)	Cohort(s), design, country	Population	Nodal status	ET/chemotherapy	Test	Percentage of patients per group						HR, low vs. high (95% CI)	p
						Low	Intermediate	High	Low	Intermediate	High		
Martin 2016, <sup>108</sup> 2014 <sup>109</sup>	GEICAM 9906, R-RCT, Spain	ER+ HER2-, (n=536)	LN1-3, 64% LN >3, 36%	<ul style="list-style-type: none"> <li>• All ET</li> <li>• All chemotherapy</li> </ul>	EndoPredict EPClin	25	75	92	6	99	87	0-10 years: 3.9 (2.0 to 7.5); p<0.0001	0-10 years: 19.4 (2.7 to 138.7); p<0.0001

ET, endocrine therapy; LN, lymph node; N+, node positive; N0, node negative.

a Full data set = all patients with EndoPredict data available; reduced data set = patients with data for all four in-scope tests analysed in TransATAC.

**TABLE 62** Additional prognostic value (likelihood ratio  $\chi^2$  values): multiple tests

Study (first author and year)	Cohort(s), design, country	Population	Nodal status	Outcome	Test or comparator <sup>a</sup>	Likelihood ratio $\chi^2$	Increase in likelihood ratio $\chi^2$ over CTS/CLP <sup>a</sup>
<b>Node negative and node positive</b>							
Sestak 2017 (data request) <sup>46</sup> (reduced data set) <sup>b</sup>	TransATAC, R-RCT, UK	<ul style="list-style-type: none"> <li>ER+ HER2–</li> <li>ET, no chemotherapy</li> <li>n = 774</li> </ul>	<ul style="list-style-type: none"> <li>LN0, 76%</li> <li>LN1–3, 24%</li> </ul>	DRFI at 10 years	EPclin	69.31 (p < 0.0001)	Over CTS: 24.39 (p < 0.0001) Over NPI: 22.17 (p < 0.0001)
					Oncotype DX	26.94 (p < 0.0001)	Over CTS: 15.22 (p = 0.0001) Over NPI: 11.89 (p = 0.0006)
					Prosigna	61.47 (p < 0.0001)	Over CTS: 26.30 (p < 0.0001) Over NPI: 23.91 (p < 0.0001)
					IHC4+C	75.30 (p < 0.0001)	Over CTS: 20.07 (p < 0.0001) Over NPI: 22.84 (p < 0.0001)
Gnant 2014, <sup>104</sup> Filipits 2014 <sup>105</sup>	ABCSG 8, R-RCT, Austria	<ul style="list-style-type: none"> <li>ER+ HER2–</li> <li>ET, no chemotherapy</li> <li>n = 1397</li> </ul>	<ul style="list-style-type: none"> <li>LN0, 71%</li> <li>LN1–3, 26%</li> <li>LN &gt; 3, 3%</li> </ul>	DRFS at 10 years	Prosigna		Over CLP: 29.94 (p < 0.0001)
<b>Node negative</b>							
Sestak 2017 (data request) <sup>46</sup> (reduced data set) <sup>b</sup>	TransATAC, R-RCT, UK	<ul style="list-style-type: none"> <li>ER+ HER2–</li> <li>ET, no chemotherapy</li> <li>n = 591</li> </ul>	LN0	DRFI at 10 years	EPclin	40.60 (p < 0.0001)	Over CTS: 15.22 (p = 0.0001) Over NPI: 17.00 (p < 0.0001)
					Oncotype DX	22.78 (p < 0.0001)	Over CTS: 10.64 (p = 0.001) Over NPI: 8.82 (p = 0.003)
					Oncotype DX RSPC	24.30 (p < 0.0001)	Over CTS: 5.10 (p = 0.02) Over NPI: 8.71 (p = 0.003)
					Prosigna	50.77 (p < 0.0001)	Over CTS: 23.71 (p < 0.0001) Over NPI: 25.54 (p < 0.0001)
					IHC4+C	48.55 (p < 0.0001)	Over CTS: 17.14 (p < 0.0001) Over NPI: 21.92 (p < 0.0001)

Study (first author and year)	Cohort(s), design, country	Population	Nodal status	Outcome	Test or comparator <sup>a</sup>	Likelihood ratio $\chi^2$	Increase in likelihood ratio $\chi^2$ over CTS/CLP <sup>a</sup>
Gnant 2014, <sup>104</sup> Filipits 2014 <sup>105</sup>	ABCSG 8, R-RCT, Austria	<ul style="list-style-type: none"> <li>ER+ HER2–</li> <li>ET, no chemotherapy</li> <li><math>n = 984</math></li> </ul>	LN0	DRFS at 10 years	Prosigna		Over CLP: 20.32 ( $p < 0.0001$ )
<b>Node positive</b>							
Sestak 2017 (data request) <sup>46</sup> (reduced data set) <sup>b</sup>	TransATAC, R-RCT, UK	<ul style="list-style-type: none"> <li>ER+ HER2–</li> <li>ET, no chemotherapy</li> <li><math>n = 183</math></li> </ul>	LN1–3	DRFI at 10 years	EPClin	12.91 ( $p < 0.001$ )	Over CTS: 7.36 ( $p = 0.007$ ) Over NPI: 5.57 ( $p = 0.02$ )
					Oncotype DX	4.75 ( $p = 0.023$ )	Over CTS: 3.56 ( $p = 0.06$ ) Over NPI: 2.14 ( $p = 0.10$ )
					Prosigna	8.51 ( $p = 0.004$ )	Over CTS: 4.39 ( $p = 0.04$ ) Over NPI: 2.71 ( $p = 0.09$ )
					IHC4+C	12.60 ( $p < 0.001$ )	Over CTS: 3.08 ( $p = 0.08$ ) Over NPI: 2.45 ( $p = 0.10$ )
Gnant 2014, <sup>104</sup> Filipits 2014 <sup>105</sup>	ABCSG 8, R-RCT, Austria	<ul style="list-style-type: none"> <li>ER+ HER2–</li> <li>ET, no chemotherapy</li> <li><math>n = 413</math></li> </ul>	<ul style="list-style-type: none"> <li>LN1–3, 89%<sup>c</sup></li> <li>LN &gt; 3, 11%<sup>c</sup></li> </ul>	DRFS at 10 years	Prosigna		Over CLP: 17.45 ( $p = 0.0002$ )

ET, endocrine therapy; N+, node positive; N0, node negative.

a Clinicopathological factors (ABCSG) = age, grade, nodal status, tumour size, Ki-67. Clinicopathological factors (GEICAM) = age, grade, nodal status, tumour size, treatment, ER, PR, Ki-67. CTS (TransATAC) and CLP (ABCSG 8) = age, grade, nodal status, tumour size, treatment. Clinicopathological factors (WSG PlanB) = nodal status, tumour stage, local grade, central grade, Ki-67, ER, PR, IHC4, oncotype DX recurrence score.

b Full data set = all patients with EndoPredict data available; reduced data set = patients with data for all four in-scope tests analysed in TransATAC.

c Nodal status for all patients; NR for HER2– subgroup.

**TABLE 63** Additional prognostic value (C-indices and multivariable analyses): multiple tests

Study (first author and year)	Cohort(s), design, country	Population	Nodal status	Outcome	Test or comparator <sup>a</sup>	C-index (AUC)	Increase in C-index (AUC) over clinicopathological factors <sup>a</sup>	Multivariable Cox proportional hazards model (adjusted for clinicopathological factors <sup>b</sup> ): HR (95% CI)
<b>Node negative and node positive</b>								
Dubsky 2013, <sup>119,120</sup>	ABCSG 6 plus ABCSG 8, R-RCT, Austria	<ul style="list-style-type: none"> <li>ER+ HER2–</li> <li>Endocrine therapy, no chemotherapy</li> <li>n = 1702</li> </ul>	<ul style="list-style-type: none"> <li>LNO, 68%</li> <li>LN+, 32%</li> </ul>	DMFS at 0–5 years	EndoPredict			1.20 (1.10 to 1.31); p < 0.001
				DMFS at 5–10 years	EndoPredict			1.28 (1.10 to 1.48); p = 0.001
					EPclin	0.786		
					EndoPredict plus AOL	0.765	EndoPredict plus AOL vs. AOL: p < 0.001	
					EndoPredict plus clinicopathological factors	0.716	EndoPredict plus clinicopathological factors vs. clinicopathological factors: p < 0.001	
	AOL	0.674						
	Clinicopathological factors	0.644						
Gnant 2014, <sup>104</sup> Filipits 2014 <sup>105</sup>	ABCSG 8, R-RCT, Austria	<ul style="list-style-type: none"> <li>ER+ HER2–</li> <li>Endocrine therapy, no chemotherapy</li> <li>n = 1397</li> </ul>	<ul style="list-style-type: none"> <li>LNO, 71%</li> <li>LN1–3, 26%</li> <li>LN &gt; 3, 3%</li> </ul>	DRFS at 10 years	Prosigna	0.720	NR	HR (intermediate vs. low) 2.15 (1.21 to 3.81); p = 0.009
								HR (high vs. low) 4.26 (2.44 to 7.43); p < 0.0001
Nitz 2017 <sup>73,74,77</sup> (n = 2642)	WSG PlanB	<ul style="list-style-type: none"> <li>100% HR+</li> <li>100% HER2–</li> <li>High clinical risk</li> <li>n = 2642</li> </ul>	<ul style="list-style-type: none"> <li>LNO, 58.8%</li> <li>LN1–3, 41.2%</li> </ul>	IDFS <sup>c</sup>	Oncotype DX	0.688		HR (25th to 75th percentile) 1.73 (1.21 to 2.47); p = 0.001
					IHC4			HR (25th to 75th percentile) NS
<b>Node negative</b>								
Gnant 2014, <sup>104</sup> Filipits 2014 <sup>105</sup>	ABCSG 8, R-RCT, Austria	<ul style="list-style-type: none"> <li>ER+ HER2–</li> <li>Endocrine therapy, no chemotherapy</li> <li>n = 984</li> </ul>	LNO	DRFS at 10 years	Prosigna	0.692	NR	
					CLP			0.639

Study (first author and year)	Cohort(s), design, country	Population	Nodal status	Outcome	Test or comparator <sup>a</sup>	C-index (AUC)	Increase in C-index (AUC) over clinicopathological factors <sup>a</sup>	Multivariable Cox proportional hazards model (adjusted for clinicopathological factors <sup>a</sup> ): HR (95% CI)
<b>Node positive</b>								
Gnant 2014, <sup>104</sup> Filipits 2014 <sup>105</sup>	ABCSG 8, R-RCT, Austria	<ul style="list-style-type: none"> <li>ER+ HER2–</li> <li>Endocrine therapy, no chemotherapy</li> <li>n = 413</li> </ul>	<ul style="list-style-type: none"> <li>LN1–3, 89%<sup>b</sup></li> <li>LN &gt; 3, 11%<sup>b</sup></li> </ul>	DRFS at 10 years	Prosigna	0.743	NR	
					CLP	0.667		
Martin 2016, <sup>108</sup> 2014 <sup>109</sup>	GEICAM 9906, R-RCT, Spain	<ul style="list-style-type: none"> <li>ER+ HER2–</li> <li>Chemotherapy-treated</li> <li>n = 536</li> </ul>	<ul style="list-style-type: none"> <li>LN1–3, 64%</li> <li>LN &gt; 3, 36%</li> </ul>	DMFS at 10 years	EPclin	0.693	1.1 (1.0 to 1.2); p = 0.003	Adding EPclin to ROR-PT plus clinicopathological factors: p < 0.001
					EndoPredict plus clinicopathological factors <sup>c</sup>	0.672		EndoPredict plus clinicopathological factors vs. clinicopathological factors: p = 0.0018
					EndoPredict	0.657		
					Clinicopathological factors <sup>a</sup>	0.654		
					ROR-PT (research-based)	0.644		Adding ROR-PT to EPclin plus clinicopathological factors: p = 0.567

ET, endocrine therapy; IDFS, invasive disease free survival; N+, node positive; N0, node negative; RS, recurrence score.

a Clinicopathological factors (ABCSG) = age, grade, nodal status, tumour size, Ki-67. Clinicopathological factors (GEICAM) = age, grade, nodal status, tumour size, treatment, ER, PR, Ki-67. CTS (TransATAC) and CLP (ABCSG 8) = age, grade, nodal status, tumour size, treatment. Clinicopathological factors (WSG PlanB) = nodal status, tumour stage, local grade, central grade, Ki-67, ER, PR, IHC4, oncotype DX RS.

b Nodal status for all patients; NR for HER2– subgroup.

c Patients treated in accordance with RS: RS < 12, no chemotherapy; RS ≥ 12, chemotherapy.

### ***EndoPredict versus EndoPredict Clinical***

Results are presented in *Table 60*. Similar proportions of low-risk patients as seen in the TransATAC cohort were reported for EPclin in ABCSG 6 plus ABCSG 8 [63% LN0–3 (additional analyses were provided in confidence by the company but cannot be reported here)]. When comparing EndoPredict with EPclin in the ABCSG 6 plus ABCSG 8 cohort, EndoPredict placed fewer patients in the low-risk category [49% for LN0–3 (additional analyses were provided in confidence by the company but cannot be reported here)] than EPclin (63%).<sup>118–120</sup> Only DRFS rates for EPclin were reported, which for low-risk patients at 5 years were 95.3%. In contrast, in the LN+ study GEICAM 9906, EndoPredict placed more patients in the low-risk category (25%) than EPclin (13%), but event rates were lower in EPclin low-risk groups (100%) than in EndoPredict (93%). HRs for EPclin were higher than for EndoPredict [e.g. 0- to 5-year HR for low vs. high 4.82 (EPclin) and 2.80 (EndoPredict)].<sup>108,109</sup>

### ***Prosigna versus EndoPredict Clinical***

Results are presented in *Table 60*. For LN0–3 cohorts, data from ABCSG 6 plus ABCSG 8<sup>118–120</sup> were consistent with TransATAC:<sup>46</sup> Prosigna/ROR-PT placed a smaller proportion of patients in the low-risk group than EPclin in both cohorts (TransATAC and ABCSG 6 plus ABCSG 8/ABCSG 8),<sup>104,105,118–120</sup> with 43% versus 61% (TransATAC) and 35% versus 63% (ABCSG trials), respectively. Additional analyses were provided in confidence by the company but cannot be reported here. This was also true in LN0 subgroups [54% vs. 73% (TransATAC)]. In LN+ subgroups, there were 8% versus 23% in TransATAC, although in the GEICAM 9906 data set,<sup>108,109</sup> the direction was reversed, with 18% versus 13%, respectively. In LN0, patients were better in Prosigna/ROR-PT than EPclin (97%<sup>46</sup> and 93.4%) in TransATAC.<sup>105</sup> In GEICAM 9906 (LN+), the direction of the event rates were reversed, at 92% and 100% at 10 years, respectively.

### ***Oncotype DX versus MammaPrint***

Results are presented in *Table 60*. Only one study reported data for both tests.<sup>57</sup> MammaPrint assigned a larger proportion of patients (63%) to the low-risk category than oncotype DX (53%) in the observational study by Russell *et al.*<sup>57</sup> Event rates were not reported, and only *p*-values for log-rank tests given, where both tests showed a statistically significant difference in DRFS at the *p* < 0.05 level for high- versus low-risk group comparisons.

### ***Oncotype DX versus IHC4 and IHC4+C***

Results are presented in *Table 60*. Two studies reported oncotype DX and IHC4 analyses [WSG PlanB<sup>73,74,77</sup> (LN0–3 only) and Gong *et al.*<sup>58</sup> (LN0 only)], and both used quartiles to define boundaries for risk categories, making the comparisons of proportions in risk categories and event rates in risk categories of little relevance to the decision problem. For IHC4 only, Gong *et al.* reported C-indices (AUC; which analyse IHC4 and oncotype DX as continuous variables) in LN0 patients, which indicate that the two tests have similar prognostic performance [oncotype DX 0.685 (95% CI 0.540 to 0.830) and IHC4 0.602 (95% CI 0.436 to 0.767)].

TransATAC<sup>46</sup> (LN0–3, LN0, LN+; see *Table 60*) reported oncotype DX and IHC+C (rather than IHC4 only), and reported similar proportions of patients in the low-risk group in LN0–3 patients (62% and 57%, respectively) and LN0 patients (63% and 66%, respectively) but not in LN+ patients (57% and 27%, respectively). In LN0 patients, 10-year DRFI was similar between the two tests in low-risk patients (94.1% and 94.7%, respectively).<sup>46</sup> HRs for low- versus high-risk patients were very similar at 5.83 compared with 6.06, respectively.<sup>46</sup> In LN+ patients, 10-year DRFI was better for IHC4+C (95.2%) than for oncotype DX (80.6%).<sup>46</sup>

### ***Impact of menopausal status***

Patients were subgrouped in accordance with menopausal status (premenopausal or postmenopausal), in GEICAM 9906.<sup>108,109</sup> For EndoPredict, event rates in the low-risk groups were similar in premenopausal and postmenopausal patients (93% and 92%, respectively), although HRs were somewhat different,

at 6.7 ( $p < 0.0001$ ) and 3.3 ( $p = 0.069$ ), respectively. For EPclin, DRFS rates in the low-risk groups were identical (100%). HRs between groups were not reported, but between-group differences were statistically significant.

### Overall survival

Data relating to OS are reported in *Table 61*. Only TransATAC<sup>46</sup> and GEICAM 9906<sup>108,109</sup> report OS. For 0–10 years in LN0–3 groups,<sup>46</sup> HRs are all statistically significant and for low-risk versus high-risk group comparisons range from 2.15 (EPclin) to 3.42 (Prosigna). In LN0 patients, HRs comparing low- with high-risk groups range from 2.06 (EPclin) to 3.64 (Prosigna). In LN+ groups, however, the low- to high-risk groups show more variation, ranging from 1.99 (EPclin) to 9.02 (Prosigna) in TransATAC, and 19.38 for EPclin in GEICAM 9906.

### Additional prognostic value

This section reports adjusted analyses, which indicate the additional prognostic value of IHC4 over clinicopathological factors. The clinicopathological factors adjusted for vary from study to study, and are detailed in the footnotes to the tables.

### Likelihood ratios

In TransATAC,<sup>46</sup> additional prognostic value was assessed via increases in likelihood ratio  $\chi^2$  for 10-year DRFI, for each test plus NPI or CTS, over NPI or CTS only (see *Table 62*). In LN0 patients, increases in likelihood ratio  $\chi^2$  over CTS and NPI were statistically significant for all tests ( $p$ -values range from  $p = 0.02$  to  $p < 0.0001$ ). Prosigna, EPclin and IHC4+C all showed greater increases (range 15.22 to 25.54) than *oncotype* DX Breast Recurrence Score or *oncotype* DX RSPC (range 5.10 to 10.64; see *Table 62*). However, for LN+ patients, increases in likelihood ratio  $\chi^2$  were much more modest (range 2.14 to 7.36 across all tests; greatest increase for EPclin), and were borderline statistically significant for all tests ( $p$ -values range from 0.10 to 0.007).

In ABCSG-8,<sup>104</sup> likelihood ratios also showed a statistically significant increase for Prosigna over the CLP (same variables as CTS) in node-negative patients ( $p < 0.0001$ ) and node-positive patients ( $p = 0.0002$ ).

### C-indices (area under the curve)

In node-positive patients in GEICAM 9906,<sup>108,109</sup> the C-index was higher for EPclin (0.693) and EndoPredict (0.657) than for the research-based ROR-PT (0.644) (see *Table 63*), although the lack of  $p$ -values and/or CIs mean that it is unclear whether or not the difference in C-indices were statistically significant. Adding EPclin to ROR-PT plus clinical variables increased the statistical significance of the test of the C-index (C-indices not reported;  $p < 0.001$ ). Conversely, adding ROR-PT to EPclin plus clinical variables did not increase the statistical significance of the test of the C-index ( $p = 0.567$ ) (see *Table 63*), although this finding should be interpreted with caution owing to the non-standard ROR-PT assay.

In ABCSG 6 plus ABCSG 8, a C-index for EPclin was only reported for a mixed node-negative and node-positive population (including 5% with more than three positive nodes) and for years 5–10 (no data for years 0–5).<sup>119</sup> In this period, the C-index statistically significantly increased when adding EndoPredict to a combination of clinical variables or to AOL (both  $p < 0.001$ ; see *Table 63*). In the ABCSG 8 analysis of Prosigna,<sup>104</sup> C-indices were numerically higher for Prosigna (0.720) than for the CLP (0.688), but any statistical significance of the difference was not reported.

### Multivariable Cox proportional hazards models

Both ABCSG 6 plus ABCSG 8<sup>118–120</sup> and GEICAM 9906<sup>108,109</sup> used multivariable analyses and showed that EndoPredict was an independent prognostic parameter for 10-year DMFS/DRFS after adjustment for clinical variables (see *Table 63*), and ABCSG 8<sup>104</sup> showed a similar finding for Prosigna.

### Discussion: studies assessing multiple tests

Few studies reported data from multiple tests and no study reported all comparisons of interest to the decision problem. Of most relevance to the decision problem was the TransATAC analysis,<sup>46</sup> as this includes patients from the UK, analyses four of the five tests, reports ER+, HER2-, LN0–3 patients only, and provides change in likelihood ratios, which allows comparisons between tests to be made. However, the TransATAC data also has limitations: it is the derivation set for IHC4 and is therefore likely to be subject to some overfitting and overestimation of prognostic performance, only menopausal patients were recruited and MammaPrint was not tested. It is also only a single cohort and ideally all comparisons would be available in multiple independent cohorts. Data from other cohorts also have limitations: ABCSG 6 plus ABCSG 8<sup>118–120</sup> only evaluated Prosigna for a proportion of patients (ABCSG 8);<sup>104,105</sup> WSG PlanB recruited only high-risk patients, and patients were treated with chemotherapy in accordance with onco $\text{type}$  DX score;<sup>73,74,77</sup> Russell *et al.*<sup>57</sup> was an observational study and reported only very limited study characteristics and analyses, Gong *et al.*<sup>58</sup> used non-standard test methods for onco $\text{type}$  DX and IHC4, and was conducted in a population of a different ethnic composition to the decision problem population; and GEICAM 9906<sup>108,109</sup> included a high proportion of LN > 4 patients (36%) and used a non-standard ROR-PT assay.

As the data comparing the tests with each other are limited, so are the conclusions that can be drawn. Broad observations include that, generally speaking, the more patients who are placed in a low-risk category, the poorer the event-free survival for that group. For example, in LN0 patients in TransATAC,<sup>46</sup> EPclin categorised 73% as low risk and these patients had a 10-year DRFI of 93.4%, and Prosigna categorised 54% as low risk and these patients had a 10-year DRFI of 97%. This effect was more pronounced in LN+ patients in TransATAC, among whom onco $\text{type}$  DX categorised 57% as low risk and these patients had a 10-year DRFI of 80.6%, and Prosigna categorised 8% as low risk and these patients had a 10-year DRFI of 100%. Another broad observation is that the tests generally perform differently in LN+ and LN0 patients. In TransATAC, both EPclin and IHC4+C tests reported lower HRs in the LN0 subgroup than in the LN+ subgroup at 10 years (EPclin LN0 HR 3.88 vs. LN+ HR 6.58; IHC4+C LN0 6.06 vs. LN+ 9.57), whereas onco $\text{type}$  DX reported higher HRs in the LN0 subgroup than the LN+ subgroup (onco $\text{type}$  DX LN0 HR 5.83 vs. LN+ HR 2.77). Data from other cohorts generally supported these broad observations.

In terms of how much additional prognostic information the tests provide over clinicopathological variables or algorithms (e.g. NPI, AOL, CTS), most data came from TransATAC,<sup>46</sup> in which increases in likelihood ratio  $\chi^2$  over CTS or NPI were statistically significant in LN0 patients across all tests (with Prosigna showing the greatest increase) and borderline significant for all tests in LN+ (with EPclin showing the greatest increase). One analysis<sup>108</sup> suggested that EPclin could provide additional information over ROR-PT (plus clinicopathological variables), whereas ROR-PT could not provide additional information over EPclin (plus clinicopathological variables), but this was limited by the use of a non-standard version of ROR-PT.<sup>108,109</sup>

### Microarray studies

Microarray studies are defined, for the purposes of this review, as any study that applied a test algorithm (e.g. onco $\text{type}$  DX, MammaPrint) to either in silico data [microarray gene expression data held electronically, usually accessed from the National Centre for Biotechnology Information (NCBI) Gene Expression Omnibus (GEO)]<sup>68</sup> or to a de novo microarray assessment conducted for the purpose of the study. These studies differ from studies that used the commercially offered assays in that the agreement between microarray and commercial assays is unknown, and, for this reason, the generalisability of the findings to the decision problem is also unknown.

It should be noted that some of the early MammaPrint studies were conducted using a 25,000-gene microarray platform, until the mini-array specific to the 70 MammaPrint genes was developed (see *Chapter 2, Development: MammaPrint*). To minimise heterogeneity between studies, MammaPrint studies conducted after the development of the mini-array that used wider microarray data are included here as 'microarray studies' rather than alongside studies using the mini-array (see *Chapter 2, Results: MammaPrint*).

Given the limitations of these studies in terms of analytic validity and owing to time constraints, we have conducted a rapid review rather than a full systematic review. This section of the report differs from other sections in that:

- No quality assessment of studies has been conducted.
- Data were not checked by a second reviewer.

It should also be noted that, owing to time and expertise constraints, the EAG was not able to fully consider the following factors:

- The degree to which the same cohorts of patients are included in multiple studies. There is likely to be considerable overlap.
- The quality of the methodology used to conduct the microarray analyses.
- The cut-off points used across the studies.
- The proportion of ER+ and HER2– patients in each cohort.
- The proportion receiving endocrine therapy or chemotherapy in each cohort.
- The ethnic composition of the cohorts used.

Further general limitations of the studies as a whole include:

- A lack of clarity as to the characteristics of the patients.
- A lack of clarity as to whether patients were treated with endocrine therapy or chemotherapy.
- A lack of clarity as to whether patients were treated in accordance with a protocol or in accordance with routine practice, and whether or not the exclusion of patients who were treated would therefore lead to spectrum bias.

Some of this information may have been obtainable by reference to the GEO, or to the primary publications relating to each cohort, but due to time constraints these data were not sought.

Although acknowledging the considerable limitations of these studies and the review methodology, microarray studies hold some value as they report data on more than one test. This is important as there are very few studies using the commercial versions of the assays that report data for more than one test (see *Appendix 5; Studies reporting more than one test*). Specifically, there are few studies that report data for MammaPrint compared with any other test, meaning that it is difficult to assess the relative merits of this test compared with others.

For this reason, the review of these studies will focus on the information provided relating to the prognostic performance and additional prognostic value of the tests in comparison with each other, rather than on absolute values provided for individual tests, which may not be generalisable. It is of course entirely possible that such comparisons between tests are not generalisable, but given the lack of data comparing the commercial tests, the information provided has some value to the decision problem.

### Microarray studies

A total of 18 studies<sup>591–608</sup> reported data from microarray analyses (*Table 64*). Of these, five reported only data for one test (three reported *oncotype DX*<sup>593,599,600</sup> and two reported *MammaPrint*<sup>592,607</sup>); the results of these studies are presented in *Report Supplementary Material 10* but are not considered further. Of the remaining 13 studies, six<sup>591,594,596–598,602</sup> reported seven cohorts of data from single institutions, five<sup>595,596,601,604,608</sup> reported pooled *in silico* data from multiple cohorts, three<sup>603,605,608</sup> reported data from METABRIC (Molecular Taxonomy of Breast Cancer International Consortium) (a UK–Canada data set), one<sup>606</sup> analysed TRANSBIG [Translating molecular knowledge into early breast cancer management: building on the BIG (Breast International Group) network for improved treatment tailoring] data (an international collaboration of 22 countries) and one analysed four previously reported cohorts<sup>605</sup> in addition to METABRIC.

TABLE 64 Characteristics of microarray studies

First author, year, number of patients	Cohorts	Country	Tests					Population	Nodal Status	ET/chemotherapy
			Oncotype DX	EndoPredict	MammaPrint	Prosigna	Other tests			
<b>Oncotype DX vs. MammaPrint vs. EndoPredict</b>										
Finetti 2014, <sup>595</sup> n = 1229	33 publicly available gene expression data sets from NCBI GEO database	NR	Yes	Yes	Yes			<ul style="list-style-type: none"> <li>ER+, HER2– NR (n = 1299)</li> <li>95% ER+, 92% HER2– (n = 3,074)</li> <li>All luminal (A or B)</li> </ul>	NR (n = 1,299)  58% LN0 (% LN > 3 NR) (n = 3,074)	NR
Zhao 2014 <sup>608</sup>  a) n = 912 a-i) n = 692 b) n = 996	a) GSE6532, GSE3494, GSE1456, GSE7390, GSE2603, E-TABM-158  b) METABRIC cohort		Yes	Yes	Yes	Excluded <sup>a</sup>		a) ER+ 76%, HER2– 85%  <ul style="list-style-type: none"><li>Subgroup:</li></ul> a-i) ER+ 100%, HER2– NR b) ER+ NR, HER2– NR	a) LN0 67% (LN > 3 NR)  a-i) NR b) NR	NR
<b>Oncotype DX vs. MammaPrint studies</b>										
Ahn 2013 <sup>591</sup>  a) n = 186 b) n = 82	Gananam Severance Hospital (1997–2007)	Korea	Yes		Yes			100% ER+ 12% HER2+  a) all patients b) subset with RS 19–30	a) 47.8% LN+ (% LN > 3 NR) b) 43.9% LN+ (LN > 3 NR)	a) 84% ET, 13% chemotherapy b) 94% ET, 82% chemotherapy
Fan 2006 <sup>594</sup> Microarray:  a) n = 295 b) Subgroup n = 225	NKI (derivation cohort for MammaPrint)	The Netherlands	Yes		Yes			a) 77% ER+  <ul style="list-style-type: none"><li>HER2 NR</li><li>Age ≤ 52 years</li><li>100% female</li></ul> b) 100% ER+	a) LN0, 51% LN1–3, 36% LN > 3, 13% b) NR	a) 14% ET, 37% chemotherapy b) NR
Jonsdottir, 2014, <sup>597</sup> n = 94	NR	Norway	Yes		Yes			a) ER+ NR  <ul style="list-style-type: none"><li>85% HER2–</li></ul> a-i) 100% ER+, HER2– NR	LN0 100% (% LN > 3 NR)	a) 14% ET, 11% chemotherapy a-i) NR
Li 2009, <sup>598</sup> n = 27	Fudan University Cancer Hospital	China	Yes		Yes			HR+ NR, 70% HER2–	LN0 56% (% LN > 3 NR)	ET NR, 100% chemotherapy

First author, year, number of patients	Cohorts	Country	Tests					Population	Nodal Status	ET/chemotherapy
			Oncotype DX	EndoPredict	MammaPrint	Prosigna	Other tests			
Györfy 2015 <sup>596</sup> a) <i>n</i> = 3534 b) <i>n</i> = 325	a) 25 data sets from GEO <sup>b</sup> b) University Hospitals (Frankfurt and Hamburg)	a) NR b) Germany	Yes		Yes			a) 83.1% ER+, 84.4% HER2+ NR Subgroup: 100% ER+, HER2- b) 81.1% ER+, HER2- NR Subgroup: i) 100% ER+; HER2- NR	a) LN+ 30.8% b) LN+ 39.4% (LN > 3 NR) Subgroup: ER+, LN0	a) ET NR, 19% chemotherapy Subgroups: i) ER+, HER2-, untreated ii) ER+, HER2-, treated b) ET and chemotherapy NR Subgroup: i) NR
Prat 2012, <sup>601</sup> <i>n</i> = 594/1380 a) <i>n</i> = 339 b) <i>n</i> = 171	GSE17705, GSE6532, GSE12093, GSE1456, MDACC133	NR	Yes		Yes	Excluded <sup>a</sup>	ER+, HER2- NR ( <i>n</i> = 549) 100% ER+ HER2- NR ( <i>n</i> = 1380)	NR ( <i>n</i> = 549) LN0 47% (% LN > 3 NR) ( <i>n</i> = 1380) a) LN0 100% b) LN+ 100%	ET 100%, chemotherapy 0%	
Tobin 2014 <sup>602</sup> a) <i>n</i> = 253 b) <i>n</i> = 159	a) Uppsala cohort b) Stockholm cohort (Karolinska Hospital)	Sweden	Yes		Yes		HR+ NR HER2- NR Subgroup: a-i) ER+ 100%	a) LN0 63% b) LN0 59%	a) ET 58%, chemotherapy 11% b) ET 72%, chemotherapy 19%	
Vollan 2015, <sup>603</sup> <i>n</i> = 1412	METABRIC	International	Yes		Yes		ER+ 100%, HER2- NR	NR	NR	
Xu 2017 <sup>604</sup> a) <i>n</i> = 917	a) METABRIC/Bioconductor data sets: GSE11121, GSE7390, GSE3494, GSE2990, Breast Cancer NKI	International	Yes		Yes	Excluded <sup>a</sup> NPI	ER+ 100%, HER2- NR	LN0 100%	NR	

continued

TABLE 64 Characteristics of microarray studies (continued)

First author, year, number of patients	Cohorts	Country	Tests				Population	Nodal Status	ET/chemotherapy
			Oncotype DX	EndoPredict	MammaPrint	Prosigna			
Ou Yang 2014 <sup>605</sup>	a) METABRIC	International; NR	Yes		Yes	Excluded <sup>a</sup>	ER+:	LN0:	NR
i) LN0 subgroup	b) Loi (GSE6532)						a) 77%	a) 52%	
ii) ER+ subgroup	c) Buffa (GSE22219)						b) 62%	b) 58%	
a) n = 1981 (1037;1526)	d) Wang (GSE19615)						c) 89%	c) 64%	
b) n = 216 (125; 134)	e) Miller (GSE3494)						d) 57%	d) 56%	
c) n = 393 (250; 348)							e) 85%	e) 67%	
d) n = 115 (64; 66)				Subgroup:	Subgroup:				
e) n = 236 (158; 201)				i) ER+ NR ii) ER+ 100%	i) LN0 100%, ii) LN0 NR				
Yin, 2014, <sup>606</sup> n = 198	TRANSBIG GSE7390	France, Sweden, UK	Yes		Yes		ER+ NR, HER2- NR	LN0 100%	ET 0%, chemotherapy 0%
						AOL NPI			

ET, endocrine therapy; LN, lymph node; NKI, Netherlands Cancer Institute; NR, not reported; RS, recurrence score.

a Cockburn 2016:<sup>609</sup> data were reported in this study for a simulation of Prosigna. However, only 45 of the 50 Prosigna genes were available for analysis and the data are excluded as they does not conform to algorithm used in the commercially offered test; Prat 2012:<sup>601</sup> ROR-P, not ROR-PT; Xu 2017:<sup>604</sup> ROR-S not ROR-PT; Ou Yang 2014:<sup>605</sup> used ROR-T and ROR-S not ROR-PT; Zhao 2014:<sup>608</sup> ROR-S only, not ROR-PT.

b GSE1456, GSE4922, GSE5327, GSE6532, GSE7390, GSE9195, GSE11121, GSE12093, GSE12276, GSE2034, GSE16391, GSE16446, GSE17705, GSE17907, GSE19615, GSE2603, GSE20685, GSE20711, GSE21653, GSE25066, GSE2990, GSE31519 and GSE3494.

All studies reported data on *oncotype DX* and *MammaPrint*, and two<sup>595,608</sup> also reported data on *EndoPredict*. For the most part, only HRs for recurrence/survival rates between test risk groups were reported, which give an indication of the test's association with an outcome, but these do not allow conclusions to be drawn about the prognostic ability of one test versus another. These data are presented in *Table 65*, and C-index (AUC) data are presented in *Table 66*, and data that provide direct comparisons of the prognostic performance of one test compared with another are presented in *Table 67*.

### Prognostic performance in microarray studies

#### Categorisation

Only four studies<sup>594,597,601,602</sup> reported the numbers of patients in each risk category, and these only included *oncotype DX* and *MammaPrint* (see *Table 65*). In LN+/LN0 cohorts for *oncotype DX*, the proportions were 24%, 31% and 37% low-risk patients, 11%, 16% and 19% intermediate-risk patients and 44%, 53% and 65% high-risk patients. In LN0 groups, the proportions were 14% and 19% low-risk patients, 19% and 45% intermediate-risk patients and 67% and 36% high-risk patients. For *MammaPrint*, the proportions were 39%, 48% and 51% low-risk patients, 61%, 52% and 49% high-risk patients in LN+/LN0 patients, and similar proportions in LN0 patients (40% and 48% low risk and 60% and 52% high risk).

#### Hazard ratios

Nine studies<sup>594–597,601–604,608</sup> reported HR data (see *Table 65*). Data for *oncotype DX* and *MammaPrint* were reported in four studies<sup>594,596,602,603</sup> with a mix of LN+/LN0 patients, LN0 only patients were reported in four studies<sup>596,597,601,604</sup> and LN+ patients in one study.<sup>601</sup> Two studies<sup>595,608</sup> reported HRs for *oncotype DX*, *MammaPrint* and *EndoPredict*.

#### *Oncotype DX versus MammaPrint: LN+/LN0*

Six studies<sup>594–596,602,603,608</sup> reported data for both *oncotype DX* and *MammaPrint* in a mixed LN+/LN0 cohort (see *Table 65*; seven cohorts/pooled cohorts analysed, including the two that also report *EndoPredict* HRs). Across various outcome measures, including DRFS, RFS, OS and BCSS, all reported statistically significant HRs between test risk groups for both tests, apart from Vollen *et al.*,<sup>603</sup> in which the HR for BCSS for *MammaPrint* was not significant [HR 1.25 (95% CI 0.95 to 1.64;  $p = 0.11$ )], and Zhao *et al.*,<sup>608</sup> which reported HRs at 5 and 10 years, and the 10-year HRs were not statistically significant. As both Zhao *et al.* and Vollen *et al.* used the METABRIC cohort, and Vollen *et al.* did not report the length of follow-up, it is possible the statistically non-significant result was for 10 or more years of follow-up. *Oncotype DX* had higher HRs in three studies (HR 2.65 vs. 1.91, 2.57 vs. 1.96 and 2.05 vs. 1.5 for *oncotype DX* vs. *MammaPrint*, respectively)<sup>595,596,602</sup> and *MammaPrint* HRs were higher in two studies (3.40 vs. 2.82 and 4.61 vs. 2.87, for *MammaPrint* vs. *oncotype DX*, respectively).<sup>596,602</sup> Whether the HR was higher in *oncotype DX* or *MammaPrint* did not appear to depend on whether the tests were analysed categorically or as continuous variables.

#### *Oncotype DX versus MammaPrint: lymph node negative*

Three studies<sup>597,601,604</sup> reported data for *oncotype DX* and *MammaPrint* in LN0 patients (see *Table 65*). Neither test was statistically significant in Jonsdottir *et al.*,<sup>597</sup> (*oncotype DX*,  $p = 0.522$ ; *MammaPrint*,  $p = 0.287$ ) when DMFS was measured at 14 years. HRs were statistically significant [HR 2.7 (95% CI not reported;  $p < 0.001$ ) and HR 2.5 (95% CI not reported;  $p < 0.001$ ), respectively] in Xu *et al.*<sup>604</sup> when RFS was measured at 15 years and in Prat *et al.*<sup>601</sup> (HR 1.97,  $p < 0.0001$ , and 1.42,  $p < 0.005$ , respectively; 95% CIs not reported), when outcomes were censored at 8.5 years. NPI was also measured in Xu *et al.*,<sup>604</sup> with a HR a little higher than *MammaPrint* and a little lower than *oncotype DX*, at 2.6 ( $p < 0.001$ ).

#### *Oncotype DX versus MammaPrint: lymph node positive*

Only one study<sup>601</sup> reported results in a subgroup of LN+ patients (see *Table 65*). Both *oncotype DX* and *MammaPrint* had statistically significant HRs [4.67 (95% CI not reported;  $p = 0.01$ ) and 2.12 (95% CI not reported;  $p = 0.03$ ), respectively].

TABLE 65 Microarray results: HRs

First author, year, number of patients	Cohorts	Population	Nodal status	ET/chemotherapy	Percentage of patients per group			Outcome	Test	Outcomes, HR (95% CI) unless stated otherwise		
					Low	Inter	High			0–5 years	0–10 years	5–10 years
<b>Oncotype DX and MammaPrint</b>												
<b>LN0/LN+</b>												
Fan 2006 <sup>594</sup> a) n = 295	NKI (derivation cohort for MammaPrint)	a) 77% ER+, HER2 NR	a) LN0, 51%, LN1–3, 36%, LN > 3, 13%	a) 14% ET, 37% chemotherapy	24	11	65	RFS	Oncotype DX	–	NR, p < 0.001	–
					39	–	61	RFS	MammaPrint	–	NR, p < 0.001	–
					24	11	65	OS	Oncotype DX	–	NR, p < 0.001	–
					39	–	61	OS	MammaPrint	–	NR, p < 0.001	–
Györfy 2015 <sup>596</sup> a) n = 3534	a) 25 data sets from GEO	a) 83.1% ER+, 84.4% HER2+ NR	a) LN+/LN0, LN+ 30.8%	a) ET NR, 19% chemotherapy	–	–	–	RFS	Oncotype DX	2.55 (2.21 to 2.94; p < 0.001)		
					–	–	–		MammaPrint	3.40 (2.47 to 4.68; p < 0.001)		
Györfy 2015 <sup>596</sup> a-i) n = 672		Subgroups a-i and ii: 100% ER+, HER2–		a-i) Untreated	–	–	–		Oncotype DX	2.82 (2.04 to 3.90; p < 0.001)		
					–	–	–		MammaPrint	3.07 (1.87 to 5.04; p < 0.001)		
Györfy 2015 <sup>596</sup> a-ii) n = 1316				a-ii) Treated	–	–	–		Oncotype DX	2.47 (2.14 to 3.49; p < 0.001)		
					–	–	–		MammaPrint	3.01 (1.85 to 4.90; p < 0.001)		
Györfy 2015 <sup>596</sup> b) n = 325	b) University Hospitals (Frankfurt and Hamburg)	b) ER+, HER2– NR	b) LN+/LN0 (LN > 3 NR)	b) ET and chemotherapy NR	–	–	–		Oncotype DX	2.65 (1.73 to 4.07; p < 0.001)		
					–	–	–		MammaPrint	1.91 (1.05 to 3.50; p = 0.0322)		
Tobin, 2014 <sup>602</sup> a) n = 253	a) Uppsala cohort	HR+ NR, HER2– NR	a) LN0 63%	a) ET 58%, chemotherapy 11%	37	19	44	BCSS	Oncotype DX	21-year follow-up: HR continuous NR; p = 0.004 Intermediate vs. low: HR NR; p = 0.018 High vs. low: HR NR; p = 0.001 High/intermediate vs. low: 2.57 (1.43 to 4.62)		
					51	–	49		MammaPrint	21-year follow-up: HR continuous NR; p = 0.005 High vs. low: 1.96 (1.21 to 3.17)		

First author, year, number of patients	Cohorts	Population	Nodal status	ET/chemotherapy	Percentage of patients per group			Outcome	Test	Outcomes, HR (95% CI) unless stated otherwise		
					Low	Inter	High			0–5 years	0–10 years	5–10 years
Tobin, 2014 <sup>602</sup> b) n = 159	b) Stockholm cohort (Karolinska Hospital)	HR+ NR, HER2– NR	b) LNO 59%	b) ET 72%, chemotherapy 19%	31	16	53		Oncotype DX	Follow-up NR: HR NR; $p=0.006$ High/intermediate vs. low: 2.87 (1.43 to 5.75)		
					48	–	52		MammaPrint	Follow-up NR: HR NR; $p<0.001$ High vs. low: 4.61 (2.12 to 10.03)		
Vollan, 2015 <sup>603</sup> n = 1412	METABRIC	ER+ 100%, HER2– NR	NR	NR	–	–	–	BCSS	Oncotype DX	Follow-up NR Intermediate vs. low: 1.23 (0.91 to 1.68; $p=0.179$ ) High vs. low: 2.35 (1.64 to 3.36; $p<0.001$ )		
					–	–	–		MammaPrint	Follow-up NR High vs. low: 1.25 (0.95 to 1.64; $p=0.11$ )		
<i>LNO</i>												
Jonsdottir, 2014 <sup>597</sup> n = 94	NR – Norway	a) ER+ NR, 85% HER2–	LNO 100%	a) 14% ET, 11% chemotherapy	19	45	36	DRFS	Oncotype DX	14-year HR Intermediate vs. low: 1.2 (0.3 to 4.4) High vs. low: 1.8 (0.5 to 6.5), $p=0.522$ Rates: low, 83%; intermediate, 79%; high, 68%		
					48	–	52		MammaPrint	14-year HR 1.6 (0.7 to 3.6; $p=0.287$ ) Rates: low, 80%; high, 71%		

continued

TABLE 65 Microarray results: HRs (continued)

First author, year, number of patients	Cohorts	Population	Nodal status	ET/chemotherapy	Percentage of patients per group			Outcome	Test	Outcomes, HR (95% CI) unless stated otherwise			
					Low	Inter	High			0–5 years	0–10 years	5–10 years	
Györfy 2015 <sup>596</sup> b-i) n = 113	b) University Hospitals (Frankfurt and Hamburg)	Subgroup b-i: 100% ER+; HER2– NR	Subgroup b-i: ER+, LNO	NR	–	–	–	RFS	Oncotype DX	Oncotype DX Sensitivity 0.80 (0.76 to 0.82) Specificity 0.55 (0.53 to 0.58) Accuracy: 0.64 (0.62 to 0.65) MammaPrint Sensitivity 0.98 (0.96 to 0.98) Specificity 0.14 (0.12 to 0.16) Accuracy: 0.47 (0.46 to 0.47)			
Prat 2012 <sup>601</sup> a) n = 339	GSE17705, GSE6532, GSE12093, GSE1456, MDACC133	100% ER+, HER2– NR	a) LNO 100%	ET 100%, chemotherapy 0%	14	19	67	DRFS	Oncotype DX	Rates: ● Low: 98% ● Intermediate: 95% ● High: 86% ● p = 0.004	DRFS censored at 8.5 years Continuous: 1.97, p < 0.0001 High vs. Low: 3.79, p < 0.0023		
					40	–	60		MammaPrint	Rates: 1. Low: 95% 2. High: 84% 3. p = 0.004	DRFS censored at 8.5 years Continuous: 1.42, p < 0.005 High vs. Low: 2.6, p = 0.0054		
Xu 2017 <sup>604</sup> a) n = 917	METABRIC/ Bioconductor data sets: GSE11121, GSE7390, GSE3494, GSE2990, breastCancerNKI	ER+ 100%, HER2– NR	LNO 100%	NR	–	–	–	RFS	Oncotype DX	15 years: 2.7 (95% CI NR; p < 0.001)			
					–	–	–		MammaPrint	15 years: 2.5 (95% CI NR; p < 0.001)			
					–	–	–		NPI	15 years: 2.6 (95% CI NR; p < 0.001)			

First author, year, number of patients	Cohorts	Population	Nodal status	ET/chemotherapy	Percentage of patients per group			Outcome	Test	Outcomes, HR (95% CI) unless stated otherwise		
					Low	Inter	High			0–5 years	0–10 years	5–10 years
<b>LN+</b>												
Prat 2012 <sup>601</sup> b) n = 171	GSE17705, GSE6532, GSE12093, GSE1456, MDACC133	100% ER+, HER2– NR	b) LN+ 100% (% LN > 3 NR)	ET 100%, chemotherapy 0%	8	12	80	DRFS	Oncotype DX	Rates: <ul style="list-style-type: none"> <li>Low: 91%</li> <li>Intermediate: 95%</li> <li>High: 72%</li> <li>p = 0.015</li> </ul>	DRFS censored at 8.5 years Continuous: 1.51, p = 0.01 High vs. Low: 4.67, p = 0.01	
					31	–	69		MammaPrint	Rates: <ul style="list-style-type: none"> <li>Low: 85%</li> <li>High: 72%</li> <li>p = 0.03</li> </ul>	DRFS censored at 8.5 years Continuous: 1.26, p = 0.06 High vs. Low: 2.12, p = 0.03	
<b>Oncotype DX and MammaPrint and EndoPredict</b>												
Finetti 2014 <sup>595</sup> n = 1229	33 publicly available gene expression data sets from NCBI GEO database	NR	LN+/LNO	NR	–	–	–	DRFS	Oncotype DX	Median follow-up: 7.8 years Intermediate vs. low: 1.82 (1.44 to 2.3; p < 0.001) High vs. low: 2.05 (1.59 to 2.63; p < 0.001)		
					–	–	–		MammaPrint	Median follow-up: 7.8 years 1.5 (1.21 to 1.85; p = 0.0002)		
					–	–	–		EndoPredict	Median follow-up: 7.8 years 1.88 (1.52 to 2.32; p < 0.001)		
Zhao 2014 <sup>608</sup> a-i) n = 692	a) GSE6532, GSE3494, GSE1456, GSE7390, GSE2603, E-TABM-158	a-i) ER+ 100%, HER2– NR	a) LNO 67% (LN > 3 NR) a-i) NR		–	–	–		Oncotype DX	1.79 (1.55 to 2.07; p < 0.0001)	0.65 (0.26 to 1.61; p = 0.3535)	1.06 (0.78 to 1.43; p = 0.7311)
					–	–	–		MammaPrint	1.70 (1.43 to 2.03; p < 0.0001)	1.06 (0.57 to 1.96; p = 0.8468)	1.16 (0.87 to 1.55; p = 0.3054)
					–	–	–		EndoPredict	1.97 (1.66 to 2.33; p < 0.0001)	1.02 (0.55 to 1.91; p = 0.9462)	1.13 (0.83 to 1.53; p = 0.4393)

continued

TABLE 65 Microarray results: HRs (continued)

First author, year, number of patients	Cohorts	Population	Nodal status	ET/chemotherapy	Percentage of patients per group			Outcome	Test	Outcomes, HR (95% CI) unless stated otherwise		
					Low	Inter	High			0–5 years	0–10 years	5–10 years
Zhao 2014 <sup>608</sup> b) n = 996	b) METABRIC cohort	b) ER+ NR, HER2– NR	b) NR		–	–	–		Oncotype DX	1.94 (1.69 to 2.24; p < 0.0001)	1.19 (0.86 to 1.65; p = 0.2856)	1.11 (0.89 to 1.38; p = 0.3481)
					–	–	–		MammaPrint	1.99 (1.63 to 2.41; p < 0.0001)	1.21 (0.87 to 1.68; p = 0.2545)	1.11 (0.89 to 1.38; p = 0.3514)
					–	–	–		EndoPredict	1.96 (1.64 to 2.33; p < 0.0001)	1.13 (0.82 to 1.55; p = 0.4593)	1.29 (1.04 to 1.59; p = 0.0183)

ET, endocrine therapy; LN, lymph node; NKI, Netherlands Cancer Institute; NR, not reported.

TABLE 66 Microarray results: C-index (AUC) data

First author, year, number of patients	Cohorts	Population	Nodal status	ET/chemotherapy	Percentage of patients per group			Outcome	Test	Outcomes
					Low	Intermediate	High			
<b>Unique cohorts</b>										
<i>Oncotype DX vs. MammaPrint</i>										
<b>LN0/LN+</b>										
Li 2009, <sup>598</sup> <i>n</i> = 27	Fudan University Cancer Hospital	HR+ NR, 70% HER2–	LN0 56%	ET NR, 100% chemotherapy	–	–	–	DFS	Oncotype DX	5-year C-index (AUC): 0.59; sensitivity 68%; specificity 50.0%
					–	–	–		MammaPrint	5-year C-index (AUC): 0.691; sensitivity 72%; specificity 66.2%
<b>Studies drawing from more than one data source, with multiple overlaps between studies</b>										
<i>Oncotype DX vs. MammaPrint studies</i>										
<b>LN0/LN+</b>										
Ahn 2013 <sup>591</sup> <i>b) n</i> = 82	Gananam Severance Hospital	100% ER+ 12% HER2+  <i>b) subset with RS 19–30</i>	<i>b) 43.9% LN+ (LN &gt; 3 NR)</i>	<i>b) 94% ET, 82% chemotherapy</i>				OS	MammaPrint vs. Oncotype DX	10 years  Oncotype DX intermediate-risk (RS 19–30) group  K–M curve: MammaPrint low vs. high: HR NR, <i>p</i> = 0.013  C-index (AUC) MammaPrint: 0.844
Prat 2012 <sup>601</sup> <i>n</i> = 1380	GSE17705, GSE6532, GSE12093, GSE1456, MDACC133	100% ER+, HER2– NR	LN0 47% (% LN > 3 NR)	ET 100%, chemotherapy 0%				DRFS	Oncotype DX vs. MammaPrint	8.5 years  Increase in LR $\chi^2$ of oncotype DX over MammaPrint: 14.4, <i>p</i> < 0.001  Increase in LR $\chi^2$ of MammaPrint over oncotype DX: 9.2, <i>p</i> = 0.002
Tobin 2014 <sup>602</sup> <i>a) n</i> = 253	a) Uppsala cohort	a-i) ER+ 100%	NR	NR				BCSS	Oncotype DX	13 years  C-index (AUC): 0.68
									MammaPrint	13 years  C-index (AUC): 0.81

continued

TABLE 66 Microarray results: C-index (AUC) data (continued)

First author, year, number of patients	Cohorts	Population	Nodal status	ET/chemotherapy	Percentage of patients per group			Outcome	Test	Outcomes
					Low	Intermediate	High			
Tobin 2014 <sup>602</sup> b) n = 159	b) Stockholm cohort (Karolinska Hospital)	HR+ NR, HER2- NR	b) LNO 59%	b) ET 72%, chemotherapy 19%	31	16	53	BCSS	Oncotype DX	14.5 years C-index (AUC): 0.72, p = NR
					48	-	52		MammaPrint	14.5 years C-index (AUC): 0.76, p = NR
Ou Yang 2014 <sup>605</sup> n = 1981 a-ii) n = 1526	a) METABRIC	ER+ 100%, HER2- NR	NR		-	-	-	BCSS	Oncotype DX	0- to 10-year C-index (AUC): 0.657, p = NR
					-	-	-		MammaPrint	0- to 10-year C-index (AUC): 0.612, p = NR
Ou Yang 2014 <sup>605</sup> b-ii) n = 134	b) Loi (GSE6532)	ER+ 100%, HER2- NR	NR		-	-	-		Oncotype DX	0- to 10-year C-index (AUC): 0.640, p < 0.05
					-	-	-		MammaPrint	0- to 10-year C-index (AUC): 0.606, p < 0.05
Ou Yang 2014 <sup>605</sup> c-ii) n = 348	c) Buffa (GSE22219)	ER+ 100%, HER2- NR	NR		-	-	-		Oncotype DX	0- to 10-year C-index (AUC): 0.727, p < 0.05
					-	-	-		MammaPrint	0- to 10-year C-index (AUC): 0.647, p < 0.05
Ou Yang 2014 <sup>605</sup> d-ii) n = 66	d) Wang (GSE19615)	ER+ 100%, HER2- NR	NR		-	-	-		Oncotype DX	0- to 10-year C-index (AUC): 0.435, p < 0.05
					-	-	-		MammaPrint	0- to 10-year C-index (AUC): 0.372, p < 0.05
Ou Yang 2014 <sup>605</sup> e-ii) n = 201	e) Miller (GSE3494)	ER+ 100%, HER2- NR	NR		-	-	-		Oncotype DX	0- to 10-year C-index (AUC): 0.645, p < 0.05
					-	-	-		MammaPrint	0- to 10-year C-index (AUC): 0.650, p < 0.05
<b>LNO</b>										
Tobin, 2014 <sup>602</sup> a) n = 253	a) Uppsala cohort	HR+ NR, HER2- NR	a) LNO 63%	a) ET 58%, chemotherapy 11%	37	19	44	BCSS	Oncotype DX	13-year C-index (AUC): 0.73
					51	-	49		MammaPrint	13-year C-index (AUC): 0.84
Prat 2012 <sup>601</sup> a) n = 610	GSE17705, GSE6532, GSE12093, GSE1456, MDACC133	100% ER+, HER2- NR	a) LNO 100%	ET 100%, chemotherapy 0%				DRFS	Oncotype DX vs. MammaPrint	8.5-year C-index (AUC): ● Oncotype DX: 0.71 ● MammaPrint: 0.64

First author, year, number of patients	Cohorts	Population	Nodal status	ET/chemotherapy	Percentage of patients per group			Outcome	Test	Outcomes
					Low	Intermediate	High			
Xu 2017 <sup>604</sup> a) <i>n</i> = 917	METABRIC/bioconductor data sets: GSE11121, GSE7390, GSE3494, GSE2990, breastCancer NKI	ER+ 100%, HER2– NR	LN0 100%	NR	–	–	–	RFS	Oncotype DX	15-year C-index (AUC): 0.68 (estimate off graph)
					–	–	–		MammaPrint	15-year C-index (AUC): 0.71 (estimate off graph)
					–	–	–		NPI	15-year C-index (AUC): 0.68 (estimate off graph)
Ou Yang 2014 <sup>605</sup> <i>n</i> = 1981 a-i) <i>n</i> = 1037	a) METABRIC	NR	LN0 100%	NR	–	–	–	BCSS	Oncotype DX	0- to 10-year C-index (AUC): 0.650, <i>p</i> = NR
					–	–	–		MammaPrint	0- to 10-year C-index (AUC): 0.641, <i>p</i> = NR
Ou Yang 2014 <sup>605</sup> b-i) <i>n</i> = 125	b) Loi (GSE6532)	NR	LN0 100%	NR	–	–	–		Oncotype DX	0- to 10-year C-index (AUC): 0.635, <i>p</i> < 0.05
					–	–	–		MammaPrint	0- to 10-year C-index (AUC): 0.604, <i>p</i> < 0.05
Ou Yang 2014 <sup>605</sup> c-i) <i>n</i> = 250	c) Buffa (GSE22219)	NR	LN0 100%	NR	–	–	–		Oncotype DX	0- to 10-year C-index (AUC): 0.681, <i>p</i> = NS
					–	–	–		MammaPrint	0- to 10-year C-index (AUC): 0.628, <i>p</i> < 0.05
Ou Yang 2014 <sup>605</sup> d-i) <i>n</i> = 64	d) Wang (GSE19615)	NR	LN0 100%	NR	–	–	–		Oncotype DX	0- to 10-year C-index (AUC): 0.665, <i>p</i> < 0.05
					–	–	–		MammaPrint	0- to 10-year C-index (AUC): 0.674, <i>p</i> = NS
Ou Yang 2014 <sup>605</sup> e-i) <i>n</i> = 158	e) Miller (GSE3494)	NR	LN0 100%	NR	–	–	–		Oncotype DX	0- to 10-year C-index (AUC): 0.608, <i>p</i> = NS
					–	–	–		MammaPrint	0- to 10-year C-index: 0.604, <i>p</i> = NS
<b>LN+</b>										
Prat 2012 <sup>601</sup> b) <i>n</i> = 699	GSE17705, GSE6532, GSE12093, GSE1456, MDACC133	100% ER+, HER2– NR	b) LN+ 100% (% LN > 3 NR)	ET 100%, chemotherapy 0%				DRFS	Oncotype DX vs. MammaPrint	0- to 10-year C-index (AUC): ● Oncotype DX: 0.64 ● MammaPrint: 0.61

continued

**TABLE 66** Microarray results: C-index (AUC) data (*continued*)

First author, year, number of patients	Cohorts	Population	Nodal status	ET/chemotherapy	Percentage of patients per group			Outcome	Test	Outcomes
					Low	Intermediate	High			
<i>Oncotype DX vs. MammaPrint vs. EndoPredict</i>										
Zhao 2014 <sup>608</sup> a) n = 912	a) GSE6532, GSE3494, GSE1456, GSE7390, GSE2603, E-TABM-158	a) ER+ 76%, HER2- 85%		NR	–	–		DRFS	Oncotype DX	Follow-up year NR for C-index analysis  C-index (AUC): 0.648 (95% CI 0.63 to 0.67)  PVE: 4.05
					–	–	–		MammaPrint	C-index (AUC): 0.612 (95% CI 0.60 to 0.63)  PVE: 4.76
					–	–	–		EndoPredict	C-index (AUC): 0.648 (95% CI 0.63 to 0.67)  PVE: 4.78

ET, endocrine therapy; K–M, Kaplan–Meier; LN, lymph node; LR, likelihood ratio; RS, recurrence score.

TABLE 67 Microarray results: additional prognostic value

Study first author and year	Cohorts	Population	Nodal status	ET/chemotherapy	Outcome	Test or comparison	Likelihood ratio $\chi^2$	Increase in likelihood ratio $\chi^2$ over clinicopathological factors <sup>a</sup>	Other analyses
<b>LN+/LN0 or NR</b>									
Ahn 2013 <sup>591</sup> b) n = 82	Gananam Severance Hospital	100% ER+, 12% HER2+ b) Subset with RS 19–30	b) 43.9% LN+ (LN > 3 NR)	b) 94% ET, 82% chemotherapy	OS	MammaPrint vs. oncoprint DX		Oncotype DX intermediate (RS 19–30) risk group  Adjusted HR <sup>a</sup> of MammaPrint: 10.19 (95% CI 1.05 to 99.01; p = 0.045)	
Fan 2006 <sup>594</sup> a) n = 295	NKI (derivation cohort for MammaPrint)	a) 77% ER+, HER2 NR	a) LN0, 51% LN1–3, 36% LN > 3, 13%	a) 14% ET, 37% chemotherapy	RFS	Oncotype DX		Adjusted HR <sup>a</sup>  Intermediate vs. low: 1.81 (95% CI 0.70 to 4.68, p = 0.22)  High vs. low: 4.27 (95% CI 2.05 to 8.92; p = 0.001)  Adjusted HR: <sup>a</sup> 3.44 (95% CI 1.98 to 5.99; p < 0.001)	
					OS	MammaPrint		Adjusted HR <sup>a</sup>	
					OS	Oncotype DX		Adjusted HR <sup>a</sup>  Intermediate vs. low: 1.81 (95% CI 0.39 to 8.27; p = 0.45)  High vs. low: 6.14 (95% CI 1.84 to 20.4; p = 0.003)  Adjusted HR: <sup>a</sup> 4.71 (95% CI 2.02 to 11.00; p < 0.001)	
Fan 2006 <sup>594</sup> b) Subgroup n = 225		b) 100% ER+	b) NR	b) NR	RFS	Oncotype DX		Adjusted HR <sup>a</sup>  Intermediate vs. low: 0.82 (95% CI 0.27 to 2.46; p = 0.72)  High vs. low: 2.59 (95% CI 1.44 to 4.65; p = 0.001)  Adjusted HR: <sup>a</sup> 3.88 (95% CI 2.15 to 7.02; p < 0.001)	
					OS	Oncotype DX		Adjusted HR <sup>a</sup>  Intermediate vs. low: 1.42 (95% CI 0.27 to 7.50; p = 0.68)  High vs. low: 4.95 (95% CI 1.82 to 13.4; p = 0.002)	
						MammaPrint		Adjusted HR: <sup>a</sup> 5.47 (95% CI 2.13 to 14.1, p < 0.001)	

continued

**TABLE 67** Microarray results: additional prognostic value (*continued*)

Study first author and year	Cohorts	Population	Nodal status	ET/chemotherapy	Outcome	Test or comparison	Likelihood ratio $\chi^2$	Increase in likelihood ratio $\chi^2$ over clinicopathological factors <sup>a</sup>	Other analyses
Zhao 2014 <sup>608</sup> a-i) n = 692	a) GSE6532, GSE3494, GSE1456, GSE7390, GSE2603, E-TABM-158	a-i) ER+ 100%, HER2– NR	a) LN0 67% (LN > 3 NR)  a-i) NR	NR	DRFS	Oncotype DX	43.6, $p < 0.0001$	23.1, $p < 0.0001^a$	
						MammaPrint	36.0, $p < 0.0001$	21.5, $p < 0.0001^a$	
						EndoPredict	53.6, $p < 0.0001$	31.4, $p < 0.0001^a$	
<b>LNO</b>									
Yin 2014 <sup>606</sup> n = 198	TRANSBIG GSE7390	ER+ NR, HER2– NR	LNO 100%	'Systemically untreated patients' <sup>b</sup>	DRFS	Oncotype DX		13.734, $p = 0.004$	
						MammaPrint		3.038, $p = 0.986$	
						AOL		3.325, $p = 0.601$	
						NPI		6.823, $p = 0.131$	
						OS			
						Oncotype DX		13.286, $p = 0.002$	
						MammaPrint		0.221, $p = 0.647$	
AOL		0.377, $p = 0.551$							
NPI		3.658, $p = 0.16$							

ET, endocrine therapy; LN, lymph node; NKI, Netherlands Cancer Institute; RFS, relapse free survival; RS, recurrence score.

a Multivariable analysis covariates. Ahn 2013: tumour size; nodal status; PR; chemotherapy treatment. Fan 2006 data set a): ER status, tumour grade, nodal status, age, tumour size, treatment (ET, chemotherapy or both). Fan 2006 data set b): as a) but omitting ER status. Zhao 2014: nodal status, grade, tumour size. Yin 2014, not adjusted, but gives values for AOL and NPI on same cohort for comparison.

b From www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE7390. (accessed 11 April 2019).

### ***Oncotype DX versus MammaPrint versus EndoPredict: lymph node positive/negative***

Two studies<sup>595,608</sup> reported two pooled analyses of 33 cohorts<sup>595</sup> and six cohorts,<sup>608</sup> and one analysis using METABRIC data (see *Table 65*).<sup>608</sup> These cohorts are likely to contain some of the same patients. All three tests reported statistically significant HRs for DRFS at time points of < 10 years, but an analysis of 0- to 5-year, 5- to 10-year and 0- to 10-year HRs in Zhao *et al.*<sup>608</sup> only reported statistically significant HRs in the period 0–5 years, for all three tests. Oncotype DX high versus low HR was the highest in the Finetti *et al.*<sup>595</sup> analysis [HR 2.05 (95% CI 1.59 to 2.63;  $p < 0.001$ )] compared with a HR for MammaPrint of 1.5 (95% CI 1.21 to 1.85;  $p = 0.0002$ ) and a HR for EndoPredict of 1.88 (95% CI 1.52 to 2.32;  $p < 0.001$ ), although when all tests were analysed as continuous variables in Zhao *et al.*,<sup>608</sup> the HR was highest for EndoPredict [1.97 (95% CI 1.66 to 2.33;  $p < 0.0001$ )] compared with MammaPrint [1.70 (95% CI 1.43 to 2.03;  $p < 0.0001$ )] and oncotype DX [1.79 (95% CI 1.55 to 2.07;  $p < 0.0001$ )].

### **C-index (area under the curve) and other comparative data**

Data relating to C-indices and other outcomes are presented in *Table 66*.

### ***Oncotype DX and MammaPrint: lymph node positive/negative***

Pairs of C-indices (AUC) for oncotype DX and MammaPrint were reported in three studies<sup>598,602,605</sup> in LN+/LNO patients (for eight cohorts). Outcomes included DRFS, DFS, OS and BCSS. The C-index ranged from 0.372<sup>605</sup> to 0.84,<sup>591,602</sup> indicating a wide range of fit. Notably, the worst fit was reported for an analysis in Ou Yang *et al.*<sup>605</sup> of cohort GSE19615, when oncotype DX had a C-index of 0.435 ( $p < 0.05$ ) and MammaPrint had a C-index of 0.372 ( $p < 0.05$ ), both indicating that the test was worse than chance alone at categorising patients into risk groups. Apart from these data, C-indices for oncotype DX ranged from 0.59<sup>598</sup> to 0.73<sup>602</sup> and for MammaPrint from 0.606 to 0.84. Oncotype DX had a higher C-index in four cohorts (METABRIC, GSE6532, GSE22219 and GSE19615),<sup>605</sup> whereas MammaPrint had a higher C-index in three (Fundan University, the Uppsala cohort and the Stockholm cohort).<sup>598,602</sup>  $p$ -values were only reported in one study<sup>605</sup> (four out of five cohorts) and were all statistically significant. 95% CIs were not reported in any analyses, meaning that it was not possible to determine if the C-indices were substantially different from each other.

One further study<sup>591</sup> reported data (see *Table 66*) that explored the prognostic value of MammaPrint in a group of patients with intermediate risk oncotype DX. MammaPrint still had prognostic value in this group, with a statistically significant difference between risk groups (HR not reported,  $p = 0.013$ ) and a C-index of 0.844, indicating that MammaPrint was able to further discriminate between patients with and without OS events.

A further study<sup>601</sup> reported increases in likelihood ratio  $\chi^2$  for oncotype DX (low-/intermediate-risk group vs. high-risk group) over MammaPrint and vice versa (see *Table 66*). This showed that the likelihood ratio  $\chi^2$  increased by 14.4 units ( $p < 0.001$ ) when oncotype was added to MammaPrint, and by 9.2 ( $p = 0.002$ ) when MammaPrint was added to oncotype DX, indicating that both tests had added prognostic value over the other, but oncotype DX added a little more.

### ***Oncotype DX and MammaPrint: lymph node negative***

Pairs of C-indices (AUC) for oncotype DX and MammaPrint were reported in four studies<sup>601,602,604,605</sup> (for eight cohorts, two of which were pooled analyses). C-indices for oncotype DX ranged from 0.608 to 0.71 and for MammaPrint from 0.604 to 0.81.  $p$ -values were only reported in one study<sup>605</sup> (five cohorts) and were not always statistically significant, possibly due to smaller sample sizes in these subgroup analyses than in the full LN+/LNO cohorts. Oncotype DX had a higher C-index in five cohorts (Prat *et al.*<sup>601</sup> and four of the cohorts reported in Ou Yang *et al.*<sup>605</sup>), and MammaPrint had a higher C-index in three (Tobin *et al.*, Xu and GSE19615 from Ou Yang *et al.*).<sup>602,604,605</sup>

### ***Oncotype DX and MammaPrint: lymph node positive***

One study<sup>601</sup> reported the C-index for LN+ patients. This was 0.64 for oncotype DX and 0.61 for MammaPrint.

## Additional prognostic value in microarray studies

### *Oncotype DX, MammaPrint and EndoPredict in lymph node-positive-negative patients*

One study<sup>594</sup> reported a multivariable analysis including *oncotype DX* and *MammaPrint* separately alongside ER status, tumour grade, nodal status, age, tumour size and treatment (endocrine therapy, chemotherapy or both) in patients with mixed nodal status (see *Table 67*). The cohort used was the derivation cohort for *MammaPrint* (and there may therefore be some overfitting of the model, resulting in overestimation of the prognostic performance for *MammaPrint*) and a subgroup of ER+–only patients. Tests were analysed as categorical rather than as continuous variables. All high versus low HRs were statistically significant, although the intermediate versus low analyses (*oncotype DX* only) were not. High versus low HRs were higher for *oncotype DX* than for *MammaPrint*, although this is perhaps to be expected as *oncotype DX* high versus low comparisons do not account for the intermediate patients, and *MammaPrint* has only two categories; the analyses are therefore not comparable.

One study reported a multivariable analysis in *oncotype DX* intermediate patients (see *Table 67*), and *MammaPrint* was shown to have additional prognostic value in this subgroup of patients (adjusted for tumour size, nodal status, PR and chemotherapy treatment) with a HR of 10.19 (95% CI 1.05 to 99.01;  $p = 0.045$ ).<sup>591</sup>

One study<sup>608</sup> reported likelihood ratio  $\chi^2$  and differences in likelihood ratio  $\chi^2$  for *oncotype DX*, *MammaPrint* and *EndoPredict* (see *Table 67*). *EndoPredict* had the highest likelihood ratio  $\chi^2$ , at 53.6 ( $p < 0.0001$ ), compared with 43.6 (*oncotype DX*) and 36.0 (*MammaPrint*) (both  $p < 0.0001$ ). In an analysis that adjusted for nodal status, grade and tumour size, the difference in likelihood ratio  $\chi^2$  over these clinicopathological variables was also highest for *EndoPredict* (31.4 vs. 23.1 and 21.5, respectively, all  $p < 0.0001$ ), indicating that all these tests have prognostic value over these clinical factors, and *EndoPredict* appears to perform best.

### *Oncotype DX and MammaPrint versus Nottingham Prognostic Index and Adjuvant! Online in lymph node negative patients*

One study reported data for LNO patients (see *Table 67*). The increase in likelihood ratio  $\chi^2$  over clinicopathological variables was reported for *oncotype DX*, *MammaPrint*, NPI and AOL. For DMFS, *oncotype DX* had the highest increase, at 13.734 ( $p = 0.004$ ), compared with *MammaPrint* (3.038,  $p = 0.986$ ), AOL (3.325,  $p = 0.601$ ) and NPI (6.823,  $p = 0.131$ ), and was the only test to report a statistically significant change. Results were similar for OS.

### **Discussion: microarray studies**

Data from microarray studies have been included in this report to provide additional information relating to the comparative prognostic value of the tests, as comparative data from studies using the commercial versions of the tests are limited in number (see *Appendix 5, Studies reporting more than one test*). In particular, comparisons between *MammaPrint* and other tests (specifically *oncotype DX* and *EndoPredict*) were made in microarray studies but rarely in the studies using the commercial tests. However, these data should be interpreted with caution because of the unknown comparability of microarray studies and the commercial versions.

Data relating to HRs for outcomes between test risk groups support the data from studies using the commercial assays that show a statistically significant difference between test risk categories for outcomes such as DRFS, DFS, OS and BCSS for *oncotype DX*, *MammaPrint* and *EndoPredict* (no microarray studies were identified assessing *Prosigna* or *IHC4*). One study did not report statistically significant HRs at  $\geq 10$  years. However, conversely, three studies reported statistically significant HRs at  $\geq 10$  years,<sup>594,602,604</sup> suggesting that the assumption of proportional hazards may not hold in all cohorts, and the tests are likely to be more often accurate at 0–5 years than at time points beyond that. HRs were generally statistically significant in LN+/LNO cohorts, LNO cohorts and LN+ cohorts, although the evidence base for the LNO cohorts and LN+ cohorts was limited and one study did not report a statistically significant HR in a LNO cohort, which may have been due to a small sample size ( $n = 94$ ) or follow-up duration (14 years).<sup>597</sup>

No study reported HRs in LN+/LN0, LN0 and LN+ patients separately, so it is difficult to draw any conclusions about whether HRs differ in accordance with lymph node status.

C-indices (AUC) were generally good for all tests, and did not appear to differ in accordance with lymph node status. Conclusions that can be drawn from the data reporting C-indices were limited by the non-reporting of 95% CIs, meaning that it was not possible to tell whether the tests were substantially better or worse than each other. One further problem with determining the superiority of tests was that *oncotype* DX has three risk categories (high, intermediate and low) whereas MammaPrint and EndoPredict have only two (high and low); C-index analyses represent the prognostic potential of the test, but do not indicate which cut-off points should be used, what clinical decisions should be made for intermediate-risk patients or what the long-term clinical outcomes would be for patients treated in accordance with the test as commercially marketed. One study showed that MammaPrint could further categorise *oncotype* DX intermediate-risk patients into high- and low-risk patients, with an excellent C-index of 0.844. However, without seeing the overall performance of MammaPrint in this cohort, it is not possible to conclude that MammaPrint outperforms *oncotype* DX. For this reason, it is difficult to draw any conclusions about superiority given these differences in categories and the clinical significance in terms of treatment options.

As in previous sections of this report, it can be argued that the true value of the test lies in how much additional prognostic information is provided over and above clinical factors. The one study<sup>608</sup> to report such data across three tests (*oncotype* DX, MammaPrint, EndoPredict) reported likelihood ratio  $\chi^2$  and change in likelihood ratio  $\chi^2$  in analyses adjusted for clinicopathological variables suggesting that EndoPredict had the greatest additional value, followed by *oncotype* DX, then MammaPrint, which agrees with the analyses reported in TransATAC. One study<sup>606</sup> (not adjusted for clinicopathological variables) in LN0 patients reported that only *oncotype* DX had a statistically significant change in likelihood ratio  $\chi^2$  whereas AOL, NPI and MammaPrint did not, which supports the order of prognostic performance reported in TransATAC.

### Conclusions: microarray studies

Microarray studies support conclusions from studies using the commercial versions of the assays in suggesting that *oncotype* DX, MammaPrint and EndoPredict can discriminate between high- and low-risk patients regardless of LN status (data limited to mixed LN+/LN0 patients for EndoPredict); the utility of the intermediate-risk group in *oncotype* DX is uncertain; the additional prognostic performance of the tests over clinicopathological variable is less certain for MammaPrint, although the order of superiority appears similar to that reported by TransATAC, namely EndoPredict, then *oncotype* DX, then MammaPrint, although the evidence base is limited.

## OPTIMA Prelim: a study of concordance between tests

### Concordance between tests

Concordance is defined in this review as the degree to which tests assign the same patients to the same risk groups. They do not report long-term outcomes. They are distinct from decision impact studies, in which patients are actually assigned to treatment or not based on the test result and clinician and patient preference.

In accordance with the scope<sup>21</sup> and the protocol,<sup>610</sup> we did not conduct a systematic review of concordance. Instead, we present a summary of one high-quality, highly relevant study [the Optimal Personalised Treatment of early breast cancer using Multi-parameter Analysis preliminary (OPTIMA Prelim) study]<sup>588</sup> conducted in the UK.

### OPTIMA Prelim: methods

The OPTIMA Prelim study (ISRCTN42400492) was a feasibility phase of Optimal Personalised Treatment of early breast cancer using Multi-parameter Analysis (OPTIMA).<sup>611</sup> OPTIMA is an ongoing trial that aims to test the effectiveness of multiparameter testing in identifying a subgroup of patients (among those who

would ordinarily be offered chemotherapy) who will not respond to chemotherapy and can therefore avoid it and move more quickly to more appropriate treatments (i.e. endocrine therapy and radiotherapy). OPTIMA Prelim was designed to help select which of six available tests [onco*type* DX, MammaPrint, Prosigna, IHC4, MammaTyper (BioNTech Diagnostics GmbH, Mainz, Germany), and NexCourse Breast by Aqua (IHC4 automated quantitative immunofluorescence-AQUA)(NexCourse Breast<sup>TM</sup>, Genoptix Inc. Carlsbad, CA, USA)] to use in the trial. Here, we only report data for the four in-scope tests (onco*type* DX, MammaPrint, Prosigna and IHC4). Three clinical prognostic scores were also used, namely AOL, NPI and Predict, but these were only compared with each other.

The OPTIMA Prelim study selected women who would routinely be offered chemotherapy, specifically women aged  $\geq 40$  years with ER+, HER2– early-stage breast cancer with either 1–9 positive lymph nodes or a tumour of  $\geq 30$  mm if node negative. Women were randomised to test-directed therapy or standard treatment (chemotherapy followed by endocrine therapy). Patients in the test-directed arm received onco*type* DX testing and those with a recurrence score of  $\leq 25$  received endocrine monotherapy.

### OPTIMA Prelim: results

Results are presented in *Table 68*. A total of 313 patients from 35 UK hospitals were recruited and randomised; 302 patients received multiple tests. Eleven patients were excluded: four withdrew consent, one was ineligible and six had insufficient tissue for all tests to be conducted.

### Nottingham Prognostic Index, Predict and Adjuvant! Online

With NPI, patients were at high (21%), intermediate (75%) and low (4%) risk. All patients with an NPI of  $\leq 3.4$  had tumours of  $\geq 30$  mm. Predict and AOL predict a risk for patients depending on whether they take only endocrine monotherapy or take chemotherapy and endocrine therapy; the difference between the Predict and AOL median predicted 10-year OS within each treatment type ranged from 6.2% to 8.4%.

### Onco*type* DX, MammaPrint, Prosigna and IHC4, MammaTyper, NexCourse Breast by Aqua

Results for all tests were available from 236 patients (78%). IHC4 could not be determined for 45 patients (15%); one patient did not have enough tissue for onco*type* DX testing, and three Prosigna and seven MammaPrint tests were unobtainable.

Out of the four in-scope tests, MammaPrint assigned the most patients to the low-risk category (61%), although when low and intermediate categories were treated as one category for the three tests that have three risk groups (onco*type* DX, Prosigna and IHC4), onco*type* DX assigned the most to the low/intermediate category (82%) and MammaPrint assigned the least (61%) (see *Table 68*).

Kappa statistics indicated modest agreement between tests, ranging from 0.33 (95% CI 0.3 to 0.5) between MammaPrint and IHC4 and 0.53 (95% CI 0.4 to 0.7) between MammaPrint and Prosigna, and 0.53 (95% CI 0.4 to 0.7) between onco*type* DX and IHC4 (see *Table 68*). Data are not reported for the four in-scope tests alone, but across all five tests (that have risk groups rather than intrinsic subtypes,

**TABLE 68** Percentage in each risk category and kappa statistics between tests

Test	Percentage tested	Percentage in risk category			Kappa statistic (95% CI)		
		Low	Intermediate	High	MammaPrint	Prosigna (L/I)	IHC4 (L/I)
Onco <i>type</i> DX	99.7	54	28	18	0.40 (0.30 to 0.5)	0.44 (0.3 to 0.5)	0.53 (0.4 to 0.7)
MammaPrint	98.9			39	–	0.53 (0.4 to 0.6)	0.33 (0.2 to 0.4)
Prosigna (L/I)	99.0	36	29	35	–	–	0.39 (0.3 to 0.5)
IHC4 (L/I)	85.1	24	48	28	–	–	–

I, intermediate; L, low.

i.e. oncotype DX, MammaPrint, Prosigna, IHC4 and IHC4-AQUA), 61% of tumours gave no consensus, and only 119 tumours (39%) were uniformly classified as either low/intermediate or high by all five tests. Of these, 93 (31%) were low/intermediate risk by all tests and 26 (8%) were high risk by all tests. An exploratory analysis using high/intermediate- versus low-risk patients also showed only moderate agreement.

The authors report a number of further analyses that demonstrate that no tests appeared to be more in agreement than others, and that there were no statistically significant differences in clinicopathological variables between concordant and discordant patients. Disagreement spanning two categories (i.e. between low and high risk) was not infrequent. Agreement was not better at the extremes of the ranges of the tests (i.e. the very low- and very high-risk tumours).

### Conclusions

The authors concluded that, although tests assigned similar proportions of patients to low/intermediate- and high-risk categories, test results for an individual patient could differ markedly depending on which test was used.



# Appendix 6 Review of existing economic analyses published since National Institute for Health and Care Excellence Diagnostics Guidance 10

## Cost-effectiveness review: methods

Systematic searches were undertaken to identify existing economic evaluations of tumour profiling tests to guide treatment decisions in people with early-stage breast cancer. Only those studies that were published since the previous appraisal of tumour profiling tests (NICE DG10<sup>20</sup>) were considered to be potentially relevant for inclusion in the review; a review and a critical appraisal of economic analyses published prior to this date is available in Ward *et al.*<sup>1</sup> The review was undertaken solely with the purpose of exploring methodological choices and their potential relevance to the current decision problem, rather than to assess the results of published economic evaluations or the potential sources of bias that might affect these.

A comprehensive search was undertaken to systematically identify economic evaluations of the five tumour profiling tests (EndoPredict, oncotype DX, MammaPrint, IHC4 and Prosigna) and reviews of economic evaluations of tumour profiling tests for breast cancer.

Literature searching for economic evaluation studies was undertaken in March 2017 in the following electronic databases:

- MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations: via Ovid, 1946 to present
- EMBASE: via Ovid, 1974 to present
- Health Technology Assessment Database: CRD, 1995 to 2016
- NHS Economic Evaluation Database: CRD, 1995 to March 2015
- Science Citation Index Expanded: Web of Science, 1900 to present
- Conference Proceedings Citation Index – Science: Web of Science, 1990 to present.

The search strategies comprised MeSH or Emtree Thesauri terms and free-text synonyms for (1) 'tumour profiling tests' and 'breast cancer' and (2) 'breast cancer' only. Searches for oncotype DX, MammaPrint, IHC4 and Prosigna were limited by publication date from 2011 (the cut-off date for the previous appraisal), whereas no date limits were applied to EndoPredict. Searches were translated across databases and were not limited by language. The search strategies are presented in *Appendix 2*. Search filters designed to identify economic evaluations and reviews were used in MEDLINE and other databases, where appropriate. Reference and citation searching of included papers was undertaken.

In order to be considered potentially relevant for inclusion in the review, studies were required to meet all of the following criteria:

- full economic evaluations comparing tumour profiling for breast cancer tests against other tests and/or current practice
- published in English
- available in full-text format (studies that were available in abstract form only were excluded from the review)
- relevant to the populations included within the final NICE scope.<sup>21</sup>

## Cost-effectiveness review results: summary of studies identified

A total of 294 potentially includable studies (including potential duplicates) were identified by the searches. Of these, 59 studies were deemed to be potentially eligible for inclusion in the review and full texts were obtained, when available. A total of 26 unique studies met the inclusion criteria and were included in the review. The scope and methodological approaches adopted within the included studies are summarised in *Tables 69* and *70*, respectively.

The models reported within the included studies were developed to assess the cost-effectiveness of tumour profiling tests across a variety of different countries including the UK, the USA, Canada, Mexico, Japan, Austria, Germany, France and the Netherlands. Most studies compared *oncotype* DX (18 studies) or MammaPrint (eight studies) against comparators such as AOL, the St Gallen guidelines, standard practice or other conventional diagnostic tools. One included study (Blank *et al.*<sup>433</sup>) compared EndoPredict against a comparator that comprised a combination of three different guidelines. There was variation between the analyses with respect to the patient populations evaluated, their disease type and other patient characteristics. The models included populations with initial ages (when reported) ranging from 45 years to 64 years.

Across the breadth of included studies, there was a high level of consistency in terms of the general modelling approach and structure, and several studies were based on a previously published model. The majority of the included models adopted a Markov or hybrid decision tree–Markov approach, with discrete nodes applied to estimate long-term costs and outcomes for patients assigned to different test risk classification categories. Two studies adopted a partitioned survival approach. One further study used a discrete event simulation approach. The structure of the model used in one study was not reported. The time horizons used in the economic models ranged from 10 years to the patient's remaining lifetime, with cycle lengths (when reported) ranging from 1 month to 1 year. Most of the models that evaluated *oncotype* DX against current practice assumed that the test was associated with a predictive benefit of chemotherapy.

Most of the included studies that adopted a Markov structure included a common set of three health states: (1) alive and recurrence-free, (2) alive with distant recurrence and (3) dead. However, several models also included other health states, such as local recurrence, disease-free after local recurrence, distant recurrence with response to treatment, distant recurrence with no response to treatment, progression of disease after distant recurrence, CHF, chronic myeloid leukaemia, AML/MDS, and febrile neutropenia and chemotherapy-induced nausea and vomiting. One model, which was reported across two studies,<sup>499,500</sup> used different health states for patients receiving endocrine therapy only (remission, local recurrence, distant recurrence and dead) and for patients receiving chemotherapy plus endocrine therapy (remission with chemotherapy, remission without chemotherapy, local recurrence, distant recurrence and dead).

Although many of the models identified by the review adopted a similar modelling approach, none included all of the relevant tests listed in the final NICE scope.<sup>21</sup> For this reason, none of the existing models included in the review was considered to be suitable for the current appraisal.

TABLE 69 Existing economic evaluations: analytic scope

First author and year	Population	Age	Intervention	Comparator	Country	Perspective	Time horizon	Discount rate
Bargallo-Rocha <sup>a</sup> (2015) <sup>430</sup>	HR+, LN0 or LN1–3 early-stage breast cancer	Baseline age 55.5 years	Oncotype DX	Current standard of care	Mexico	Instituto Mexicano del Seguro Social perspective	40 years	5%
Holt <sup>a</sup> (2013) <sup>141</sup>	LN0 or pN1mi, ER+ breast cancer in the UK	Mean age 60.55 years	Oncotype DX	Conventional diagnostic procedures (including AOL and NPI)	UK	NHS	30 years	3.5%
Davidson <sup>a</sup> (2013) <sup>478</sup>	ER+ LN0 breast cancer	Mean age 53 years	Oncotype DX	Conventional diagnostic procedures	Canada	Canadian health-care system	Lifetime (up to maximum age of 100 years)	5%
Jahn (2015) <sup>618</sup>	ER+ and/or PR+, <i>HER2</i> /neu negative, and LN0 breast cancer	Baseline age 50 years	Oncotype DX	AOL score	Austria	Societal perspective in line with the Austrian health-care system	Lifetime	5%
Kondo (2011) <sup>440</sup>	ER+ early-stage breast cancer	Baseline age 45 years	Oncotype DX	St Gallen criteria	Japan	Societal	Lifetime (with assumptions about maximum survival after 10 1-year cycles)	3%
Lamond (2012) <sup>362</sup>	Early-stage, endocrine-sensitive breast cancer undergoing adjuvant chemotherapy or no chemotherapy	Median age 50 years	Oncotype DX	Current practice (population-based study)	Canada	Canadian health-care system perspective	25 years	3%
Paulden (2013) <sup>619</sup>	LN0, ER+ and/or PR+ ( <i>HER2</i> -/neu) early-stage breast cancer patients who are candidates for adjuvant chemotherapy	Baseline age 50 years	Oncotype DX	AOL	Canada	Ontario Ministry of Health and Long-Term Care	Lifetime	5%
Reed <sup>a</sup> (2013) <sup>620</sup>	LN0, ER+ breast cancer	Baseline age 55 years	Oncotype DX	No RS-guided strategy	USA	US health-system perspective and societal perspective	Lifetime	3%
Blank <sup>a</sup> (2015) <sup>433</sup>	ER+, <i>HER2</i> -breast cancer	Median age appears to be 64 years	EndoPredict (EPclin) ± three guidelines	Three guidelines (German S3, St Gallen, NCCN)	Germany	German health-care system	Lifetime (50 years)	3%
Bonastre (2014) <sup>434</sup>	LN0 early-stage breast cancer. Subgroup analysis of ER+ patients	Patients aged < 61 years	MammaPrint	AOL, chemotherapy for all	France	French National Insurance Scheme	10 years	4%
Retèl <sup>a</sup> (2012) <sup>621</sup>	Early, operable, LN0, ER+ breast cancer	Baseline age 50 years	MammaPrint	Clinical-pathological guidelines (such as AOL)	The Netherlands	Dutch health-care perspective	20 years	4% costs, 1.5% health outcomes
Retèl <sup>a</sup> (2012) <sup>622</sup>	Early, LN0 breast cancer	Not reported	MammaPrint; <i>oncotype</i> DX	AOL	The Netherlands	Dutch health-care perspective	20 years	4% costs, 1.5% health outcomes
Retèl <sup>a</sup> (2013) <sup>623</sup>	Early LN0 ER+ breast cancer after local therapy	Baseline age 50 years	MammaPrint 70G-FFT; MammaPrint 70G-PAR	AOL	The Netherlands	Societal perspective	20 years	4% costs, 1.5% health outcomes
Retèl <sup>a</sup> (2013) <sup>624</sup>	Reflective of RASTER population	Mean age 48 years	MammaPrint	AOL	The Netherlands	Dutch health-care perspective	20 years	4% costs, 1.5% health outcomes

continued

**TABLE 69** Existing economic evaluations: analytic scope (*continued*)

First author and year	Population	Age	Intervention	Comparator	Country	Perspective	Time horizon	Discount rate
Hall (2012) <sup>438</sup>	LN+, ER+ early-stage breast cancer	Baseline age 60 years	Oncotype DX	Standard care (chemotherapy for all)	UK	NHS	Lifetime (up to maximum age of 100 years)	3.5%
Hannouf (2012) <sup>499</sup>	Early-stage ER+/PR+ axillary LN0 breast cancer	Starting age unclear	Oncotype DX	Current practice (population-based study)	Canada	Canadian public health-care system	Lifetime	5%
Hannouf (2014) <sup>500</sup>	Postmenopausal women with early-stage ER+/PR+ axillary LN+ breast cancer	Mean age 61 years	Oncotype DX	Current practice	Canada	Canadian public health-care system	Lifetime	5%
Kondo (2012) <sup>625</sup>	HR+, LN0, HER2- early-stage breast cancer	Baseline age 55 years	MammaPrint	St Gallen criteria	Japan	Societal	10 years	3%
Mislick <sup>a</sup> (2014) <sup>626</sup>	Early-stage, LN0, ER+ breast cancer	Not reported	Mammostrat	Oncotype DX	USA	Third-party payer perspective	10 years	3%
Stein (2016) <sup>207</sup>	ER+, HER2- early-stage breast cancer patients	Median age 58 years	Oncotype DX; MammaPrint/Bluetest; Prosigna	Chemotherapy for all	UK	NHS	Lifetime (up to maximum age of 100 years)	3.5%
Tiwana (2013) <sup>627</sup>	Women who are LN0, ER+ and/or PR+, HER2/neu-negative early-stage breast cancer, who are candidates for adjuvant chemotherapy	50 years	Oncotype DX	AOL	Canada	Not reported – appears to be payer perspective	Lifetime	5%
Vanderlaan <sup>a</sup> (2011) <sup>628</sup>	Minimally LN+, early-stage breast cancer	Mean age 62 years	Oncotype DX	Current care (US NCCN guidelines)	USA	US payer (managed care) perspective	30 years	3%
Wong (2012) <sup>629</sup>	Women with LN+ HR+ breast cancer (one to three nodes)	Reflective of RxPONDER <sup>630</sup>	Oncotype DX	Current care (US NCCN guidelines)	USA	Payer	Lifetime (40 years)	3%
Ward (2013) <sup>1</sup>	Women with ER+ LN0, and HER2- early-stage breast cancer	Mean age 58.3 years	Oncotype DX, IHC4, MammaPrint and Mammostrat (Mammostrat, Clariant Diagnostic Services, Inc, Aliso Viejo, CA, USA)	Current clinical practice	UK	NHS and PSS	Lifetime (up to age of 100 years)	3.5%
Yang <sup>a</sup> (2012) <sup>631</sup>	LN0, ER+ breast cancer	Not reported	Oncotype DX	MammaPrint	USA	Third party payer	10 years	3%
Yamauchi <sup>a</sup> (2014) <sup>247</sup>	Women with ER+, LN0 (including micrometastases) ESBC who were eligible for treatment with adjuvant chemotherapy after having undergone surgery for primary tumour removal and lymph node dissection	Mean age 49.8 years	Oncotype DX	No RS guided strategy	Japan	Societal	Lifetime	3%

ESBC, early-stage breast cancer; FFT, fresh frozen tissue; RS, recurrence score; RxPONDER, Rx for Positive Node, Endocrine Responsive breast cancer.

a Known or potential conflict of interest declared.

**TABLE 70** Existing economic evaluations: modelling approach and assumptions regarding predictive benefit and chemotherapy

First author and year	Model approach	Cycle length	Model type	Does model claim predictive benefit for test?	Assumptions on chemotherapy use	Long-term health states
Bargalló-Rocha (2015) <sup>430</sup>	Markov	1 year	Classification to LR, IR, HR	Yes – RRR only in the high-risk group, based on Paik <sup>50</sup>	Proportion of all groups receive chemotherapy	3 states: 1. recurrence-free 2. recurrence 3. dead
Holt (2013) <sup>141</sup>	Markov	1 year	Classification to LR, IR, HR	Yes – RRRs in intermediate and high risk based on Paik <sup>50</sup>	Change in chemotherapy use informed by decision conflict analysis (changes applied to all three risk groups)	3 states: 1. recurrence-free 2. recurrence 3. dead
Davidson (2013) <sup>218</sup>	Markov	1 year	Classification to LR, IR, HR	Yes – different RRRs between risk groups	Proportion of all groups receive chemotherapy	5 states: 1. RFS no chemotherapy 2. RFS chemotherapy 3. distant recurrence no chemotherapy 4. distant recurrence post chemotherapy 5. dead
Jahn (2015) <sup>618</sup>	DES	N/A	Sequential use of AOL and onco $type$ DX – eight test strategies considered	Yes	Chemotherapy provided to proportion of patients in all groups except AOL low risk and onco $type$ DX low risk	DES includes: 1. recurrence-free 2. distant recurrence 3. death
Kondo (2011) <sup>440</sup>	Markov	Unclear – appears to be 1 year	Reclassification based on use of assay	Yes	Half of cases with no definitive indication undergo adjuvant chemotherapy and only cases with high RS undergo chemotherapy after the use of the assay based on the results of Japanese validation study	5 states: 1. ER+, ESBC after adjuvant therapy 2. distant recurrence with response to treatment 3. distant recurrence with no response to treatment 4. progression of disease after distant recurrence 5. death

continued

**TABLE 70** Existing economic evaluations: modelling approach and assumptions regarding predictive benefit and chemotherapy (*continued*)

First author and year	Model approach	Cycle length	Model type	Does model claim predictive benefit for test?	Assumptions on chemotherapy use	Long-term health states
Lamond (2012) <sup>362</sup>	Markov	1 month	Classification to LR, IR, HR	Yes – only in low risk and high risk	For no test, based on Canadian population-based study; for test, based on RS. Usage in intermediate group assumed to be the same in both groups	10 states: <ol style="list-style-type: none"> <li>1. chemotherapy</li> <li>2. CINV</li> <li>3. FN</li> <li>4. disease-free</li> <li>5. local relapse</li> <li>6. distant relapse</li> <li>7. treated local relapse</li> <li>8. AML/MDS</li> <li>9. CHF</li> <li>10. dead</li> </ol>
Paulden (2013) <sup>619</sup>	Markov	Appears to be monthly	Reclassification based on use of assay	Yes	Different regimens assumed for different risk groups. Different proportions of patients assumed to receive chemotherapy in accordance with risk group (estimated by linear regression)	5 states: <ol style="list-style-type: none"> <li>1. risk classification</li> <li>2. adjuvant chemotherapy</li> <li>3. no distant recurrence</li> <li>4. distant recurrence</li> <li>5. dead</li> </ol>
Reed (2013) <sup>620</sup>	Markov	6 months	Classification based on RS	Yes – different RRR assumed in each risk group	No low risk get chemotherapy, all intermediate risk and high risk get chemotherapy	3 states: <ol style="list-style-type: none"> <li>1. disease-free</li> <li>2. distant recurrence</li> <li>3. dead</li> </ol>
Blank (2015) <sup>433</sup>	Markov	1 year	Based on sensitivity and specificity of test/guideline	No – same treatment effect applied to all groups irrespective of risk	No chemotherapy for low-risk patients	3 states: <ol style="list-style-type: none"> <li>1. disease-free</li> <li>2. distant recurrence</li> <li>3. dead</li> </ol>

LR modelled implicitly

First author and year	Model approach	Cycle length	Model type	Does model claim predictive benefit for test?	Assumptions on chemotherapy use	Long-term health states
Bonastre (2014) <sup>434</sup>	EEACT with partitioned survival	Unclear	Unclear	No – authors state that there is no evidence to support predictive benefit for MammaPrint	For MammaPrint and AOL, only high-risk patients were assumed to receive chemotherapy. For the all chemotherapy comparator, all patients receive chemotherapy irrespective of risk	4 states: <ol style="list-style-type: none"> <li>1. post surgery with chemotherapy (disease-free)</li> <li>2. first year post surgery without chemotherapy (disease-free)</li> <li>3. DRFS</li> <li>4. dead</li> </ol>
Retèl (2012) <sup>621</sup>	Markov	1 year	Based on sensitivity and specificity of test/guideline	Unclear	Chemotherapy used only in high-risk patients in accordance with treatment guidelines	4 health states: <ol style="list-style-type: none"> <li>1. DFS</li> <li>2. relapse (including local and regional recurrences, secondary primary and contralateral breast cancer)</li> <li>3. metastasis</li> <li>4. dead</li> </ol>
Retèl (2012) <sup>622</sup>	Markov	1 year	Based on sensitivity and specificity of test/guideline	Unclear	High and intermediate groups combined – both assumed to receive ET plus chemotherapy	4 health states: <ol style="list-style-type: none"> <li>1. DFS</li> <li>2. relapse (including local and regional recurrences, secondary primary and contralateral breast cancer)</li> <li>3. metastasis</li> <li>4. dead</li> </ol>
Retèl (2013) <sup>623</sup>	Markov	1 year	Based on sensitivity and specificity of test/guideline	Unclear	Chemotherapy used only in high-risk patients in accordance with treatment guidelines	Not reported but based on previous 4-state model reported by Retèl <i>et al.</i> <sup>621</sup> (see above)
Retèl (2013) <sup>624</sup>	Markov	Not reported, but likely to be 1 year	Based on sensitivity and specificity of test/guideline	Unclear	Not reported but likely to be same as other Retèl studies	4 health states: <ol style="list-style-type: none"> <li>1. DFS</li> <li>2. relapse (including local and regional recurrences, secondary primary and contralateral breast cancer)</li> <li>3. metastasis</li> <li>4. dead</li> </ol>

continued

**TABLE 70** Existing economic evaluations: modelling approach and assumptions regarding predictive benefit and chemotherapy (*continued*)

First author and year	Model approach	Cycle length	Model type	Does model claim predictive benefit for test?	Assumptions on chemotherapy use	Long-term health states
Hall (2012) <sup>438</sup>	Decision tree and modified Markov model	Not reported	Classification to LR or HR	Unclear – data contained within the appendices appear to suggest that predictive benefit is modelled	All high-risk patients receive chemotherapy	6 health states: <ol style="list-style-type: none"> <li>1. disease-free</li> <li>2. distant recurrence</li> <li>3. local recurrence</li> <li>4. disease-free after local recurrence</li> <li>5. CHF</li> <li>6. dead</li> </ol>
Hannouf (2012) <sup>499</sup>	Markov	1 month	Classification to LR, IR, HR with separate Markov nodes for chemotherapy plus ET vs. ET only (accounting for chemotherapy-related AEs)	Unclear – appears to assume predictive benefit	Model assumes that 50% of intermediate-risk patients receive chemotherapy	ET-only model – 4 states: <ol style="list-style-type: none"> <li>1. remission</li> <li>2. local recurrence</li> <li>3. distant recurrence</li> <li>4. dead</li> </ol> Chemotherapy plus ET model – 5 states: <ol style="list-style-type: none"> <li>1. remission with chemotherapy SAEs</li> <li>2. remission without chemotherapy SAEs</li> <li>3. local recurrence</li> <li>4. distant recurrence</li> <li>5. dead</li> </ol>

First author and year	Model approach	Cycle length	Model type	Does model claim predictive benefit for test?	Assumptions on chemotherapy use	Long-term health states
Hannouf (2014) <sup>500</sup>	Markov	1 month	Classification to LR, IR, HR with separate Markov nodes for chemotherapy plus ET vs. ET alone (accounting for chemotherapy-related AEs)	Unclear – appears to assume predictive benefit	Model assumes that 50% of intermediate-risk patients receive chemotherapy	ET-only model – 5 states: <ol style="list-style-type: none"> <li>1. remission</li> <li>2. local recurrence</li> <li>3. distant recurrence</li> <li>4. dead</li> </ol> Chemotherapy plus ET model – 5 states: <ol style="list-style-type: none"> <li>1. remission with chemotherapy SAEs</li> <li>2. remission without chemotherapy SAEs</li> <li>3. local recurrence</li> <li>4. distant recurrence</li> <li>5. dead</li> </ol>
Kondo (2012) <sup>625</sup>	Markov	1 year	Classification to LR, HR	No	Chemotherapy applied to HR, ET only for low-risk patients	5 states: <ol style="list-style-type: none"> <li>1. ER+, LN0, HER2– early-state breast cancer after adjuvant chemotherapy</li> <li>2. distant recurrence responded to treatment</li> <li>3. distant recurrence not responded to treatment</li> <li>4. progression of disease after distant recurrence</li> <li>5. dead</li> </ol>
Mislick (2014) <sup>626</sup>	Markov	1 year	Classification to LR, IR, HR	Yes – for both Mammostrat and oncotype DX	80% HR assumed to receive chemotherapy; 10% low risk assumed to receive chemotherapy; 50% intermediate risk assumed to receive chemotherapy	3 states: <ol style="list-style-type: none"> <li>1. no recurrence</li> <li>2. recurrence</li> <li>3. dead</li> </ol>

continued

**TABLE 70** Existing economic evaluations: modelling approach and assumptions regarding predictive benefit and chemotherapy (*continued*)

First author and year	Model approach	Cycle length	Model type	Does model claim predictive benefit for test?	Assumptions on chemotherapy use	Long-term health states
Stein (2016) <sup>207</sup>	Decision tree and modified Markov model	1 year	Classification to LR or HR	Separate analyses undertaken including predictive benefit and assuming constant benefit across risk groups	All high-risk patients receive chemotherapy	7 health states: 1. disease-free 2. distant recurrence 3. local recurrence 4. disease-free after local recurrence 5. CHF 6. chronic myeloid leukaemia 7. dead
Tiwana (2013) <sup>627</sup>	Not reported – appears to be Markov	Not reported	Classification to low–low risk, low–intermediate risk, low–high risk, low–none risk, intermediate–low risk, intermediate–intermediate risk intermediate–high risk, intermediate–none risk, high–low risk, high–intermediate risk, high–high risk or high–none risk. Based on a model constructed for the Ontario Health Technology Assessment Committee	Yes – different recurrence rates modelled between groups and tests	Based on usage reported in Asad <i>et al.</i> <sup>632</sup>	Not reported – appears to include 3 states:  relapse-free  distant metastases  dead
Vanderlaan (2011) <sup>628</sup>	Appears to be Markov	Not reported	Classification to LR or HR. Original source model provided by Cedar Associates based in California, USA	No – same recurrence rates for all HR patients	71% of women in usual care assumed to receive chemotherapy treatment	3 states: 1. non-progressed disease 2. progressed disease 3. death
Wong (2012) <sup>629</sup>	Decision tree with partitioned survival approach to determine sojourn time	Not reported	For patients whose treatment decision was based on US NCCN criteria classification to LR or HR. For patients whose treatment was based on the oncotype DX test results classification to LR, IR or HR	Yes – different treatment effects applied for each risk category	≈55% of women assumed to receive chemotherapy	Not clearly reported – appears to be 3 states: 1. disease-free 2. relapsed 3. dead

First author and year	Model approach	Cycle length	Model type	Does model claim predictive benefit for test?	Assumptions on chemotherapy use	Long-term health states
Ward (2013) <sup>1</sup>	Markov	6 months	Classification to risk/prognosis group	No	Baseline chemotherapy use (without test) based on English cancer registry data. Use of chemotherapy conditional on test based on unpublished data	4 states: 1. recurrence-free 2. distant recurrence 3. long-term AEs (AML) 4. dead  Local recurrence included as event
Yang (2012) <sup>631</sup>	Markov	1 year	Classification to LR or HR using AOL and reclassification probabilities from the literature	Yes – different risk reductions applied between HR and LR	90% of patients who were high risk in accordance with both AOL and <i>oncotype</i> DX/MammaPrint received chemotherapy, 90% of patients who were at low risk in accordance with both AOL and <i>oncotype</i> DX/MammaPrint did not receive chemotherapy. For patients who experienced a conflicting result between AOL and <i>oncotype</i> DX/MammaPrint, 50% of the subpopulation received chemotherapy	3 states: 1. no recurrence 2. recurrence 3. dead
Yamauchi (2014) <sup>247</sup>	Markov	Unclear – appears to be 1 year	Classification to LR, IR, HR	Yes – different risk reductions applied between risk groups	Based on empirical study (Yamauchi <i>et al.</i> <sup>247</sup> )	3 states: 1. no recurrence 2. recurrence 3. dead

CINV, chemotherapy-induced nausea and vomiting; DES, discrete event simulation; EEA, Economic evaluation alongside a clinical trial; ESBC, early-stage breast cancer; ET, endocrine therapy; FN, febrile neutropenia; HR, high risk; IR, intermediate risk; LR, low risk; RFS, recurrence-free survival; N/A, not applicable; RRR, relative risk reduction; RS, recurrence score; SAE, serious adverse event.



## Appendix 7 Review and critical appraisal of economic analyses provided by test manufacturers

Economic analyses were provided by the manufacturers of onco $type$  DX (Genomic Health) and MammaPrint (Agendia) and the chief investigator of the EndoPredict (Myriad Genetics) decision impact study.<sup>62,94,159,182</sup> The fully executable health economic models developed for the analyses of onco $type$  DX and MammaPrint were made available to the EAG; the model referred to in the draft EndoPredict cost-effectiveness paper was not provided to the EAG. These three analyses are detailed and critically appraised in the following sections.

### Agendia cost-effectiveness report: MammaPrint versus current practice

Agendia submitted a model, which was critiqued by the EAG as part of the assessment process, but it cannot be reported here as Agendia withdrew permission to reproduce the model.

### Genomic Health dossier: onco $type$ DX versus current practice

The Genomic Health dossier made available to NICE and the EAG includes a cost-effectiveness report detailing the methods and results of a de novo health economic evaluation of onco $type$  DX versus current practice for early-stage breast cancer in the UK.<sup>62</sup> The fully executable economic model was also made available to the EAG for scrutiny.

### Genomic Health model scope

According to the Genomic Health dossier,<sup>62</sup> the model was based on the previous analysis reported by Ward *et al.*<sup>1</sup> The company's base-case model evaluates the cost-effectiveness of onco $type$  DX versus current practice in ER+ LN0 patients. The model also allows for the evaluation of onco $type$  DX versus MammaPrint, EndoPredict and Prosigna as secondary analyses. The base case includes ER+, LN0 early-stage breast cancer patients, with the option to evaluate LN+ patients as a secondary analysis. Cost-effectiveness results are expressed in terms of the incremental cost per QALY gained. Health outcomes and costs are discounted at a rate of 3.5% per annum. Costs are valued at 2016 prices and reflect a NHS and PSS perspective.

### Genomic Health model structure

The company's model is referred to as a Markov model in the Genomic Health dossier, but is more accurately described as a hybrid decision tree–Markov model. The decision tree portion of the model incorporates the decision to give adjuvant chemotherapy or not. Within the onco $type$  DX group, this probability is driven by the onco $type$  DX Breast Recurrence Score, and in the comparator group, this probability is driven by current clinical practice as recorded in the pre-onco $type$  DX chemotherapy decision in the NHS England onco $type$  DX Access Scheme Data set.<sup>183</sup>

The Markov component of the model includes three health states: (1) recurrence free, (2) distant recurrence and (3) dead. The model adopts a 30-year time horizon and a 6-month cycle length. The age of patients on entry into the model is 58.9 years, based on the mean age of patients in the NHS England Access Scheme Database.<sup>183</sup> Patients can die from breast cancer or from other causes. The model assumes that onco $type$  DX is predictive of chemotherapy benefit, hence different treatment effects are applied in accordance with the low, intermediate and high recurrence score groups (applied to the onco $type$  DX group only). Health utilities are assigned to the recurrence-free and distant recurrence states. A chemotherapy-related disutility is applied during each cycle for those who receive chemotherapy in either the test or no-test group. A further QALY loss is applied for women who experience local recurrence. Separate health utility values are

applied for patients who develop AML and for those in the final 3 months of life prior to death due to breast cancer. As the model does not contain separate health states for these two states, the health utility values for patients in the recurrence-free and distant recurrence health states are adjusted to account for the lower health utility values for patients with AML and for those dying from breast cancer.

The costs used in the Genomic Health model were based on Ward *et al.*;<sup>1</sup> these were uplifted to current values using the HCHS pay and prices inflation index.<sup>195</sup> According to the Genomic Health dossier, all patients are assumed to receive endocrine therapy, based on the following assumptions:

- tamoxifen for 5 years (40% of patients)
- anastrozole for 5 years (20% of patients)
- letrozole for 5 years (20% of patients)
- tamoxifen for 2 years plus exemestane for 3 years (20% of patients)
- tamoxifen for 5 years followed by letrozole for a further 3 years (half of patients completing tamoxifen for 5 years received an additional 3 years of letrozole) (10% of patients).

The model assumes that adjuvant chemotherapy consists of six cycles of FEC75 (5 fluorouracil, epirubicin and cyclophosphamide). The cost of chemotherapy is included as a once-only cost and includes the costs of drug acquisition, administration, monitoring and an echocardiogram for 25% of patients undergoing chemotherapy (total chemotherapy cost = £4678). The model includes costs associated with the following short-term AEs: anaemia (1.4%), thrombocytopenia (0.3%), neutropenic infection (1.6%), nausea/vomiting (24.2%) and stomatitis (4%). This cost is applied as a once-only cost of £315 for women receiving adjuvant chemotherapy. A proportion of women receiving chemotherapy (0.46%) are assumed to subsequently develop AML; this is included as a once-only cost of £13,123. Half of the annual cost of distant recurrence (half of £9316) is applied to patients in the distant recurrence health state during each cycle. A once-only cost (£16,127) of treating local recurrence is applied to 10.5% of patients entering the distant recurrence state. The model also includes a cost of £4608 to reflect end-of-life costs for women who die as a consequence of their breast cancer.

The Genomic Health model makes the following structural assumptions:

- The results of the *oncotype* DX test are assumed to be predictive of the benefit deriving from subsequent chemotherapy use. Conversely, a common relative ROR is applied to all patients in the current practice group.
- Survival following distant recurrence is assumed to be 3.3 years (based on Thomas *et al.*<sup>186</sup>).
- A HRQoL decrement associated with AEs is applied during every model cycle for the remaining lifetime of patients who receive adjuvant chemotherapy.
- The costs of short-term AEs are included only in the first model cycle.
- AML is included as a long-term complication of chemotherapy.
- All patients are assumed to receive endocrine therapy.

### **Evidence sources used to inform the Genomic Health model**

Table 71 summarises the evidence sources used to inform the Genomic Health model.

### **Probability of receiving chemotherapy under current practice and with *oncotype* DX**

Data from the NHS England Access Scheme on the use of *oncotype* DX from 2015/16<sup>183</sup> were used to model the levels of chemotherapy use resulting from the use of *oncotype* DX and from the use of standard practice. These data were provided as AiC and cannot be reported here.

**TABLE 71** Evidence sources used in the Genomic Health model

Parameter	Source	EAG comments
10-year risk of distant recurrence on endocrine therapy	Dowsett <i>et al.</i> <sup>37</sup>	Estimates presented in the Genomic Health dossier and model do not match the estimates in the Dowsett <i>et al.</i> <sup>37</sup> paper
Oncotype DX recurrence score classification	NHS England Access Scheme Database <sup>183</sup>	Risk classification probabilities and risk of distant recurrence are not derived from the same source. This may produce a bias due to differences in the distribution of prognostic variables for patients within each recurrence score category between the two sources. Risk reclassification is applied incorrectly in the model
Relative risk reduction associated with chemotherapy	Paik <i>et al.</i> <sup>50</sup>	This is applied incorrectly within the standard care group in a way that suggests that the same patient receiving the same treatment accrues a different level of benefit if they are tested with oncotype DX
Probability patient receives chemotherapy	NHS England Access Scheme Database <sup>183</sup>	This source reflects the LNO 'intermediate-risk' group only
Health utilities	Ward <i>et al.</i> <sup>1</sup>	Health losses due to chemotherapy-related AEs are applied incorrectly
Probability of short-term AEs during the first 6 months	Ward <i>et al.</i> <sup>1</sup>	–
Probability of local recurrence	Ward <i>et al.</i> <sup>1</sup>	–
Probability of AML	Ward <i>et al.</i> <sup>1</sup>	–
Other-cause mortality rates	ONS <sup>190</sup>	–
Oncotype DX cost	Genomic Health <sup>62</sup>	–
All other costs	Ward <i>et al.</i> <sup>1</sup>	–

ONS, Office for National Statistics.

### Risk of distant recurrence

The 10-year risk of distant recurrence in accordance with oncotype DX Breast Recurrence Score was taken from Dowsett *et al.*,<sup>37</sup> the proportion of patients in each recurrence score category is common to both modelled groups (Table 72). Based on the assumptions employed in the model reported by Ward *et al.*,<sup>1</sup> the ROR is tapered to be 50% of the estimated risk during years 11–15 and 0% thereafter. The RR of distant recurrence for chemotherapy versus no chemotherapy is taken from Paik *et al.*<sup>50</sup> Within the oncotype DX group, it is assumed that the oncotype DX test is predictive of chemotherapy benefit. As shown in Table 72, the RR applied is dependent on the oncotype DX risk group, with the largest treatment effect applied in the high recurrence score group. In contrast, within the standard care group, the model assumes that the RR associated with chemotherapy is constant across all patients.

**TABLE 72** Risk of distant recurrence and the benefit (RR) of chemotherapy

Oncotype DX recurrence score risk groups	Risk of distant recurrence (no chemotherapy) (Dowsett <i>et al.</i> 2010 <sup>37</sup> ) (%)	RR with chemotherapy	
		Standard care	Oncotype DX
Low RS	9	82.7	1.00 <sup>a</sup>
Intermediate RS	16	82.7	0.61
High RS	23	82.7	0.26

RS, recurrence score.  
a Assumed value.

### Node-positive patients

The Genomic Health dossier includes a secondary analysis that explores the use of *oncotype* DX in ER+ LN+ patients. The main differences between this analysis and the base-case LNO analysis are summarised in *Table 73*. The proportion of patients receiving chemotherapy in the *oncotype* DX group was based on *Loncaster et al.*,<sup>145</sup> which resulted in a 69.2% reduction in chemotherapy following the use of the test. It should be noted that unlike the base case, the analysis in the LN+ population did not use DRFS to estimate chemotherapy benefit; instead, DFS rates were derived from *Albain et al.*<sup>53</sup> (this same approach is used within the EAG's sensitivity analyses). The dossier states that only RRs for chemotherapy that were statistically significant were used; if this statement was accurate, this would result in a RR of 1.0 for the low recurrence score and intermediate recurrence score group and 0.59 in the high recurrence score group. However, the Genomic Health model inputs do not reflect this: all reported RRs were used, irrespective of whether or not they were associated with a statistically significant difference (see *Table 73*).

### Comparison of *oncotype* DX and other tests (*MammaPrint*, *EndoPredict score*, *EndoPredict Clinical* and *Prosigna*)

In order to estimate the proportion of patients receiving chemotherapy in the comparator group, data on concordance between *oncotype* DX and the comparator tests were used to recategorise patients in the NHS England Access Scheme Database.<sup>183</sup> The proportions of patients receiving chemotherapy in each *oncotype* DX Breast Recurrence Score group are shown in *Table 74*. For *MammaPrint*, concordance data from *Shivers et al.*,<sup>401</sup> a US study with 135 patients, were used. For *EndoPredict*, data from *Varga et al.*,<sup>410</sup> a small study of 24 patients in Germany and Switzerland, were used. For *Prosigna*, a US study of 52 patients was used.<sup>462</sup> For *MammaPrint*, *EndoPredict* and *Prosigna*, it was assumed that 100% of high-risk and 0% of low-risk patients in the comparator group would receive chemotherapy, and, for *Prosigna*, 50% of the intermediate-risk group were assumed to receive chemotherapy. With the exception of the comparator test cost, all other parameters were held at the base-case values.

**TABLE 73** Parameter values in the LN+ analysis

Population	Percentage receiving chemotherapy		10-year cumulative probability of distant recurrence (no chemotherapy) (%)	RR with chemotherapy	
	Current practice group	<i>Oncotype</i> DX group		Current practice	<i>Oncotype</i> DX
Low RS	100	7.5	40	0.72	1.02
Intermediate RS	100	63.2	51	0.72	0.72
High RS	100	83.3	57	0.72	0.59

RS, recurrence score.

**TABLE 74** Parameter values for *MammaPrint*, *EndoPredict score*, *EPclin* and *Prosigna*

<i>Oncotype</i> DX RS group	Proportion of patients	Proportion of patients receiving chemotherapy by test (%)			
		<i>MammaPrint</i>	<i>EndoPredict score</i>	<i>EPclin</i>	<i>Prosigna</i>
Low RS	Confidential information has been removed	29	40	27	26
Intermediate RS	Confidential information has been removed	51	80	50	38
High RS	Confidential information has been removed	86	100	67	50

RS, recurrence score.

### Results of the Genomic Health model

The Genomic Health deterministic base-case analysis indicates that onco $type$  DX produces positive health gains [0.03 life-years gained (LYGs) and 0.07 QALYs] at an additional cost of (confidential information has been removed); this corresponds to an ICER of (confidential information has been removed) per QALY gained. The results are driven by an overall reduction in chemotherapy levels in women with a low or intermediate onco $type$  DX Breast Recurrence Score (who benefit less from chemotherapy) and an increase in chemotherapy levels in those with a high onco $type$  DX Breast Recurrence Score (who benefit more from chemotherapy). The company's probabilistic results indicate that the modelled estimates of incremental QALYs and costs are associated with considerable uncertainty. The cost-effectiveness plane generated using the Genomic Health model shows a wide dispersion of results, with a substantial number of samples being in the north-west quadrant (dominated) and the south-east quadrant (dominating). It should be noted that the cost-effectiveness plane presented in Figure 6 of the Genomic Health<sup>62</sup> dossier appears very different from that generated by the EAG using the model; the reasons for this are unclear. The CEAC generated using the model suggests that the probability that onco $type$  DX produces more net benefit than current practice at WTP thresholds of £20,000 and £30,000 per QALY gained is approximately 0.51 and 0.52, respectively. The EAG has concerns regarding the robustness of the company's probabilistic ICER as different model runs produced very different results, ranging from < £10,000 per QALY gained to > £170,000 per QALY gained.

The results for the LN+ population and for the LNO population comparing onco $type$  DX with the other four tests are presented in *Table 75*. These analyses consistently indicate that, using mean values, onco $type$  DX dominates the comparators. As with the LN+ analysis, the cost-effectiveness plane presented in the Genomic Health<sup>62</sup> dossier (Figure 6) shows a wide dispersion of results, with a large proportion of samples in the north-west (dominated) and south-east (dominating) quadrants.

The company's one-way sensitivity analyses (not shown) indicate that the model results are sensitive to changes in several parameter values including the time horizon, the discount rate, the disutility associated with chemotherapy and current levels of chemotherapy use.

The EAG notes that given that most of the probabilistic samples suggest that onco $type$  DX either dominates or is dominated by current practice, it is surprising that none of the DSAs indicate this result.

### Critical appraisal of the Genomic Health model

The EAG has several concerns regarding the Genomic Health model (*Box 1*). In particular, the EAG identified a number of programming errors within the model. As a consequence, the EAG does not consider the results of the Genomic Health model to be robust. The EAG's concerns are discussed in more detail in the following sections.

#### Use of inappropriate structural assumptions that bias in favour of onco $type$ DX

The Genomic Health model assumes that the onco $type$  DX test is predictive of chemotherapy benefit. As shown in *Table 72*, this results in the RR for distant recurrence being dependent on the onco $type$  DX Breast Recurrence Score category, with the greatest chemotherapy benefit being applied to the high recurrence score group. In the model, the standard care arm mirrors the onco $type$  DX arm in that patients are also split into the three onco $type$  DX Breast Recurrence Score categories. The difference between the arms is the proportion of patients in each risk group who go on to receive adjuvant chemotherapy. However, as shown in *Table 72*, the RR used in the standard care arm is constant across all three risk groups and is based on the crude average of the three RRs reported in the Paik *et al.*<sup>50</sup> study. The distribution of patients between the three recurrence score groups differs between the NHS England Access Scheme Database<sup>183</sup> used in the Genomic Health model and the Paik *et al.*<sup>50</sup> study and, therefore, the crude mean RR from Paik *et al.* does not represent the average RR for the population in the Genomic Health model. Furthermore, as onco $type$  DX only identifies patients who may benefit from chemotherapy, the same RR of distant recurrence by recurrence score category should be applied to both the modelled onco $type$  DX and current practice groups (by recurrence score score), as each group has exactly the same

**TABLE 75** Results of the Genomic Health model: oncotype DX vs. standard care and other comparator tests

Option	LYGs	QALYs	Costs	Incremental LYGs	Incremental QALYs	Incremental costs	ICER (per QALY gained)
<b>Analysis 1: LN0 – comparison vs. standard care</b>							
Oncotype DX	12.82	10.50	Confidential information has been removed	0.03	0.07	Confidential information has been removed	Confidential information has been removed
Standard care	12.80	10.43	Confidential information has been removed	–	–	–	–
<b>Analysis 2: LN+ comparison vs. standard care</b>							
Oncotype DX	12.95	10.60	Confidential information has been removed	–0.05	0.15	Confidential information has been removed	Dominating
Standard care	13.00	10.44	Confidential information has been removed	–	–	–	–
<b>Analysis 3: LN0 – comparison with MammaPrint</b>							
Oncotype DX	12.82	10.50	£6319	0.02	0.07	–£1272	Dominating
MammaPrint	12.80	10.43	£7590	–	–	–	–
<b>Analysis 4: LN0 – comparison vs. EndoPredict score alone</b>							
Oncotype DX	12.82	10.50	£6139	0.01	0.08	–£762	Dominating
EndoPredict	12.82	10.41	£7081	–	–	–	–
<b>Analysis 5: LN0 – comparison vs. EPclin score</b>							
Oncotype DX	12.82	10.50	£6319	0.03	0.06	–£532	Dominating
EndoPredict	12.80	10.44	£6850	–	–	–	–
<b>Analysis 6: LN0 – comparison vs. Prosigna</b>							
Oncotype DX	12.82	10.50	£6319	0.03	0.06	–£655	Dominating
Prosigna	12.79	10.44	£6974	–	–	–	–

**BOX 1** Main issues relating to the Genomic Health model identified by the EAG

- Use of inappropriate structural assumptions that bias in favour of *oncotype* DX.
- Inappropriate application of chemotherapy-related disutility over remaining patient lifetime.
- Risk classification probabilities and distant recurrence rates derived from separate sources.
- Application of NHS England Access Scheme Database to all LNO patients.
- Model errors.

patient distribution across recurrence score scores. If a patient is identified by *oncotype* DX as being high risk, the benefit they accrue from adjuvant chemotherapy should be identical to that accrued by the same patient who receives chemotherapy without the test.

### **Inappropriate application of chemotherapy-related disutility over remaining patient lifetime**

The QALY decrement resulting from the use of chemotherapy is applied during every cycle for the remainder of the modelled patients' lifetimes. The EAG considers it unlikely that patients would suffer the adverse effects of adjuvant chemotherapy years after they have completed their treatment. This represents a very pessimistic assumption that increases the overall reduction in QALYs associated with chemotherapy and overestimates the benefits associated with reducing overall chemotherapy use.

### **Risk classification probabilities and distant recurrence rates derived from separate sources**

The risk of distant recurrence and the proportion of patients in each *oncotype* DX Breast Recurrence Score category were taken from two separate studies (Dowsett *et al.*<sup>37</sup> and the NHS England Access Scheme Database<sup>183</sup>). The use of separate sources for these inputs may produce confounding due to differences in the characteristics of patients within each recurrence score category between the two sources. In addition, the EAG notes that the risk of distant recurrence in the Genomic Health model does not match the 9-year risk of distant recurrence for LNO patients presented in Dowsett *et al.*<sup>37</sup> or the Genomic Health<sup>62</sup> dossier.

### **Application of NHS England Access Scheme Database to all lymph node-negative patients**

The NHS England Access Scheme Database<sup>183</sup> is only applicable to women who are at clinical intermediate-risk based on the NPI or other clinical indicators. However, it is unclear from the Genomic Health dossier whether the model applies only to this population or whether the model is intended to reflect costs and outcomes of the *oncotype* DX test across the whole LNO population.

### **Model errors**

The EAG identified an error in the company's calculations relating to the proportion of patients in the low-, intermediate- and high-risk groups who receive chemotherapy. The correct proportions are presented in the model; however, these are not applied directly but are instead incorrectly adjusted when used to calculate the traces for the Markov nodes (confidential information has been removed).<sup>183</sup> This error leads to a substantial underestimate of the number of patients receiving chemotherapy in both the intermediate- and high-risk groups and has a significant impact on the model results.

In addition, the results reported for the node-positive patients in the Genomic Health model could not be replicated by the EAG using the data described in the Genomic Health dossier. In order to replicate the results, two different sets of data were required. For the risk of distant recurrence, the Dowsett *et al.*<sup>37</sup> used in the base-case analysis had to be selected (rather than the appropriate Albain *et al.*<sup>53</sup> study). In addition, the results in the dossier use Paik *et al.*<sup>50</sup> (rather than the appropriate Albain *et al.*<sup>53</sup> study).

The impact of correcting the major errors in the Genomic Health model is explored further through comparison with the EAG model in *Chapter 3, Comparison between the Genomic Health model, the current External Assessment Group model and the previous External Assessment Group model (lymph node negative, clinical intermediate-risk subgroup)*.

### ***EndoPredict draft cost-effectiveness paper (Myriad Genetics)<sup>182</sup>***

#### **Model scope**

The chief investigator of the EndoPredict decision impact study<sup>159</sup> made available a draft manuscript that outlines the methods and results of an economic analysis comparing of EPclin plus AOL versus AOL only in women with ER+, HER2– early-stage breast cancer, having had an intermediate-risk score using AOL. The EAG notes that the AOL risk interval is not explicitly defined. The executable model was not made available, hence the EAG was unable to verify whether it has been implemented appropriately.

The manuscript presents two sets of analyses: (1) a short-term cost-minimisation analysis of EPclin versus usual practice (including only chemotherapy acquisition costs and the costs of providing the EPclin test), and (2) a cost-effectiveness analysis of EndoPredict plus AOL versus AOL only from the perspective of the NHS over a lifetime horizon. Most of the details of the Myriad model<sup>182</sup> were provided in confidence and cannot be reported here.

#### **Results of the Myriad model**

The cost-minimisation analysis suggests that EndoPredict led to a small but non-statistically significant increase in the mean per-patient cost of acquisition and provision of chemotherapy to the NHS of £149.

The cost-effectiveness analysis suggests that the ICER for EndoPredict plus AOL versus AOL is £26,836 per QALY gained.<sup>182</sup>

The critical appraisal of the Myriad model was held as confidential and cannot be reported here.

### ***Summary of economic evidence made available to the External Assessment Group***

The EAG has concerns regarding the economic evidence for oncotype DX and EndoPredict that was made available to it. In particular, the Genomic Health model for oncotype DX includes a number of errors and, in the opinion of the EAG, unreasonable assumptions. The EAG did not receive a model for EndoPredict and, therefore, cannot comment fully on the reliability of the results presented. No economic evidence was provided by the manufacturers of Prosigna or IHC4. Agendia submitted a model, which was critiqued by the EAG as part of the assessment process, but it cannot be reported here as Agendia withdrew permission to reproduce the model.

## Appendix 8 External Assessment Group model input parameter tables

**TABLE 76** Risk classification probabilities using oncotype DX, Prosigna, IHC4+C and EPclin (TransATAC)

Test (number of samples)	Proportion of patients with risk classification <sup>a</sup>		
	Low	Intermediate	High
<b><i>LNO NPI ≤ 3.4</i></b>			
Oncotype DX (541)	0.72	0.24	0.04
Prosigna (410)	0.72	0.24	0.03
IHC4+C (510)	0.88	0.11	0.01
EPclin (423)	0.90	–	0.10
<b><i>LNO NPI &gt; 3.4</i></b>			
Oncotype DX (284)	0.50	0.31	0.19
Prosigna (253)	0.27	0.38	0.35
IHC4+C (279)	0.36	0.38	0.25
EPclin (254)	0.47	–	0.53
<b><i>LN1–3</i></b>			
Oncotype DX (219)	0.57	0.32	0.11
Prosigna (192)	0.08	0.32	0.60
IHC4+C (213)	0.28	0.34	0.38
EPclin (198)	0.24	–	0.76

<sup>a</sup> Values may not sum to 1.0 due to rounding errors.

**TABLE 77** Risk classification probabilities using MammaPrint (MINDACT)

Population	Proportion of patients with risk classification	
	MammaPrint low risk	MammaPrint high risk
MINDACT ITT population ( <i>n</i> = 6693)	0.64	0.36
MINDACT mAOL clinical high-risk subgroup ( <i>n</i> = 3370)	0.46	0.54
MINDACT mAOL clinical high-risk subgroup ( <i>n</i> = 3324)	0.82	0.18

**TABLE 78** The 10-year distant recurrence rates by risk classification for oncotype DX, Prosigna, IHC4+C and EPclin

Population	10-year DMFI (95% CI)			
	Oncotype DX <sup>a</sup>	Prosigna	IHC4+C	EPclin
LNO, NPI ≤ 3.4, low risk	0.983 (0.963 to 0.992)	0.986 (0.962 to 0.995)	0.975 (0.954 to 0.987)	0.971 (0.947 to 0.984)
LNO, NPI ≤ 3.4, intermediate risk	0.931 (0.867 to 0.965)	0.933 (0.857 to 0.969)	0.878 (0.747 to 0.943)	N/A
LNO, NPI ≤ 3.4, high risk	0.838 (0.577 to 0.945)	0.636 (0.297 to 0.845)	0.800 (0.204 to 0.969)	0.870 (0.714 to 0.944)
LNO, NPI > 3.4, low risk	0.854 (0.776 to 0.907)	0.923 (0.825 to 0.967)	0.873 (0.787 to 0.926)	0.848 (0.761 to 0.905)
LNO, NPI > 3.4, intermediate risk	0.798 (0.694 to 0.869)	0.796 (0.687 to 0.870)	0.788 (0.688 to 0.859)	N/A
LNO, NPI > 3.4, high risk	0.749 (0.598 to 0.851)	0.699 (0.584 to 0.788)	0.769 (0.645 to 0.855)	0.774 (0.688 to 0.838)
LN1–3, low risk	0.818 (0.727 to 0.880)	1 (N/A)	0.961 (0.851 to 0.990)	0.95 (0.811 to 0.988)
LN1–3, intermediate risk	0.754 (0.630 to 0.842)	0.807 (0.679 to 0.889)	0.758 (0.635 to 0.845)	N/A
LN1–3, high risk	0.686 (0.447 to 0.839)	0.707 (0.604 to 0.788)	0.672 (0.546 to 0.771)	0.716 (0.629 to 0.785)

N/A, not applicable.

<sup>a</sup> Equivalent data relating to RPSC (oncotype DX plus clinicopathological factors) were also provided by the study investigators. The cost-effectiveness of this option is explored within the sensitivity analyses.

**TABLE 79** Calculation of 5-year DMFS probabilities by clinical/genomic risk group and chemotherapy use

Randomised group	Treatment	EAG group label <sup>c</sup>	Number randomised before genomic correction	Number randomised after genomic correction	Number in group <sup>a</sup>	Percentage of overall trial population	5-year DMFS (%)	5-year cumulative DMFS probability (%)	Distant metastases event rate (year)	10-year DMFS probability for group	6-month recurrence probability for group
mAOL low risk, MammaPrint low risk	Chemotherapy	A	2634	2745	37	0.55	97.60	2.40	0.005	0.953	0.002
	No chemotherapy	B			2708	40.46	97.60	2.40	0.005	0.953	0.002
mAOL high risk, MammaPrint low risk	Chemotherapy	C	1497	1550	793	11.85	95.90	4.10	0.008	0.920	0.004
	No chemotherapy	D			757	11.31	94.40	5.60	0.012	0.891	0.006
mAOL low risk, MammaPrint high risk	Chemotherapy	E	690	592	296	4.42	95.80	4.20	0.009	0.918	0.004
	No chemotherapy	F			296	4.42	95.00	5.00	0.010	0.903	0.005
mAOL high risk, MammaPrint high risk	Chemotherapy	G	1873	1806	1735	25.92	90.60	9.40	0.020	0.821	0.010
	No chemotherapy	H			71	1.06	90.60	9.40	0.020	0.821 <sup>b</sup>	0.010

a Based on Cardoso *et al.*<sup>98</sup> supplementary material, Table S11.

b Adjusted 10-year DMFS without chemotherapy estimated to be 0.766.

c EAG group labels are described on p.113 of the EAG report.

**TABLE 80** Baseline chemotherapy probabilities by risk group [provided by NCRAS (Dr Kwok Wong, Senior Cancer Analyst, National Cancer Registration and Analysis Service, 28 June 2017)]

Group	Age (years)					
	55–75			≤ 75		
	ACT	No ACT	Percentage	ACT	No ACT	Percentage
LN0, NPI ≤ 3.4	329	4248	7.19	964	6008	13.83
LN0, NPI > 3.4	1388	2081	40.01	3265	2897	52.99
LN1–3	1849	1099	62.72	4557	1526	74.91

ACT, adjuvant chemotherapy.

**TABLE 81** Summary of post-test chemotherapy probabilities conditional on risk classification

Source	Population	Proportion of patients receiving adjuvant chemotherapy conditional on test risk classification		
		Low risk	Intermediate risk	High risk
NHS England Access Database <sup>183</sup>	LN0, intermediate clinical risk	0.01	0.33	0.89
Holt <i>et al.</i> <sup>201</sup>	LN0 or pN1mic	0.07	0.59	0.91
Bloomfield <i>et al.</i> <sup>159</sup>	Unclear	0.07	N/A	0.77
Loncaster <i>et al.</i> <sup>145</sup>	LN0	0.02	0.51	0.85
	LN+	0.08	0.63	0.83
UKBCG survey (three-level tests)	LN0, NPI ≤ 3.4	0.00	0.17	0.74
	LN0, NPI > 3.4	0.04	0.41	0.92
	LN1–3	0.46	0.76	0.95
UKBCG survey (two-level tests)	LN0, NPI ≤ 3.4	0.01	N/A	0.71
	LN0, NPI > 3.4	0.15	N/A	0.92
	LN1–3	0.40	N/A	0.97

N/A, not applicable.

**TABLE 82** Estimates of adjuvant chemotherapy benefit applied in the EAG model

Test risk group	10-year RR of distant recurrence: chemotherapy vs. no chemotherapy		
	EAG base case: oncotype DX, Prosigna, EPclin, IHC4+C, non-predictive (EBCTCG <sup>199</sup> )	EAG sensitivity analysis: oncotype DX, predictive benefit (Paik <i>et al.</i> <sup>50</sup> and Albain <i>et al.</i> <sup>53</sup> )	EAG base case: MammaPrint MINDACT population, non-predictive (Cardoso <i>et al.</i> <sup>98</sup> )
<b>LN0 subgroups (NPI ≤ 3.4 and NPI &gt; 3.4)</b>			
Low risk	0.76	1.31 <sup>a</sup>	–
Intermediate risk	0.76	0.61 <sup>a</sup>	–
High risk	0.76	0.26 <sup>a</sup>	–

**TABLE 82** Estimates of adjuvant chemotherapy benefit applied in the EAG model (*continued*)

Test risk group	10-year RR of distant recurrence: chemotherapy vs. no chemotherapy		
	EAG base case: oncotype DX, Prosigna, EPclin, IHC4+C, non-predictive (EBCTCG <sup>199</sup> )	EAG sensitivity analysis: oncotype DX, predictive benefit (Paik <i>et al.</i> <sup>50</sup> and Albain <i>et al.</i> <sup>53</sup> )	EAG base case: MammaPrint MINDACT population, non-predictive (Cardoso <i>et al.</i> <sup>98</sup> )
<b>LN1–3 subgroup</b>			
Low risk	0.76	1.02 <sup>a,b</sup>	–
Intermediate risk	0.76	0.72 <sup>a,b</sup>	–
High risk	0.76	0.59 <sup>a,b</sup>	–
<b>MINDACT ITT population</b>			
MammaPrint low risk	–	–	0.77
MammaPrint high risk	–	–	0.77
<b>MINDACT mAOL low risk</b>			
MammaPrint low risk	–	–	0.84
MammaPrint high risk	–	–	0.84
<b>MINDACT mAOL high risk</b>			
MammaPrint low risk	–	–	0.74
MammaPrint high risk	–	–	0.74
<p>a Deterministic values applied in the sensitivity analyses are also adjusted by half of the variance, derived from reported 95% CIs.</p> <p>b HRs treated as RRs.</p>			

**TABLE 83** Summary of EQ-5D health state valuations in identified studies

Author	Publication type	Country	Population	Health state description	EQ-5D valuation for health state
Farkkila <i>et al.</i> <sup>204</sup>	Abstract	Finland	778 breast cancer patients aged 31–90 years in the Hospital District of Helsinki and Uusimaa	Baseline	0.818 (SD 0.228)
				First year of remission	0.860 (SD 0.178)
				Following years after remission	0.843 (SD 0.189)
				Metastatic disease	0.746 (SD 0.251)
				Palliative patients	0.514 (SD 0.300)
Lidgren <i>et al.</i> <sup>191</sup>	Paper	Sweden	361 consecutive breast cancer patients attending the breast cancer outpatient clinic at Karolinska University Hospital Solna for outpatient visits between April and May 2005	First year after primary breast cancer <sup>a</sup>	0.696 (95% CI 0.634 to 0.747)
				First year after recurrence	0.779 (95% CI 0.700 to 0.849)
				Second and following years after primary breast cancer/recurrence	0.779 (95% CI 0.745 to 0.811)
				Metastatic disease	0.685 (95% CI 0.620 to 0.735)

continued

**TABLE 83** Summary of EQ-5D health state valuations in identified studies (*continued*)

Author	Publication type	Country	Population	Health state description	EQ-5D valuation for health state
Naik <i>et al.</i> <sup>206</sup>	Paper	Canada	1759 ambulatory cancer survivors at the Princess Margaret Cancer Centre (mixed cohort with various cancer types, 282 patients with breast cancer)	Breast local/regional	0.82 (SE 0.01)
				Breast distant/metastatic	0.75 (SE 0.03)
Yousefi <i>et al.</i> <sup>205</sup>	Paper	Iran	163 patients with breast cancer who attended the breast cancer subspecialty clinic affiliated with the Breast Cancer Research Center (BCRC), in Tehran, Iran	First year after primary breast cancer	0.674 (SD 0.201)
				First year after recurrence	0.718 (SD 0.139)
				Second and following years after primary breast cancer/recurrence	0.730 (SD 0.221)
				Metastatic disease	0.552 (SD 0.227)

SD, standard deviation.

a Lidgren *et al.*<sup>191</sup> also report EQ-5D utility scores for patients receiving adjuvant hormone therapy of 0.824 ( $n = 79$ , 95% CI 0.785 to 0.857).

**TABLE 84** Health utilities applied in the EAG model

Health state/event	Duration applied in model	Mean utility	SE	Source
Recurrence free	Indefinite	0.824	0.018	Lidgren <i>et al.</i> <sup>191</sup>
Distant metastases	Indefinite	0.685	0.029	
Disutility distant metastases	Indefinite	-0.14	0.11	Calculated using difference method
Local recurrence	Once-only QALY loss applied on transition to distant recurrence state	-0.108	0.04 (assumed)	Campbell <i>et al.</i> <sup>193</sup>
Chemotherapy AEs	Once-only QALY loss applied in first cycle	-0.038	0.004 (assumed)	
AML	Indefinite	0.26	0.04 (assumed)	Younis <i>et al.</i> <sup>192</sup>

**TABLE 85** Test costs assumed in the EAG analysis

Test	Cost	Comments
Oncotype DX (excluding PAS)	£2580	Tests carried out in Genomic Health laboratory in USA. Cost includes sample handling and customer service
Prosigna <sup>a</sup>	£1970	NanoString Technologies submitted a cost per Prosigna test based on conducting the test in a NHS laboratory, which included the laboratory costs (£240), the list price for Prosigna kits (£1650), cost of the nCounter System (£194,600) and was based on 2500 samples per lifetime of the nCounter System
EndoPredict <sup>a</sup>	£1500	Tests carried out in Myriad's laboratory in Munich
IHC4	£203	IHC4 submitted a document outlining the time and equipment necessary to conduct the test in 2014 prices. The total cost of the test (£198) was uplifted using the HCHS index <sup>195</sup>
MammaPrint	£2326	Converted from Euros to UK Pounds Sterling assuming an exchange rate of 1.15

a Alternative costs per test due to NHS testing explored in sensitivity analyses.

**TABLE 86** Adjuvant chemotherapy costs applied in the EAG model

Regimen	Proportion of women receiving regimen	Costs								
		Central line	Drug	Delivery	Supportive medicines	Medical oncology	Specialist nurse review	Blood tests	Toxicity	Total
FEC100-T (3 + 3 cycles)	0.25	£18.17	£306.84	£1284.58	£435.64	£450.03	£613.10	£62.32	£378.20	£3548.88
TC (4 cycles)	0.20	£18.17	£52.80	£856.39	£15.91	£310.81	£408.74	£41.55	£144.83	£1849.19
FEC75 (6 cycles)	0.45	£18.17	£346.38	£1284.58	£80.77	£310.81	£613.10	£62.32	£245.91	£2962.05
FEC100-Pw (3 + 3 cycles)	0.10	£18.17	£274.53	£2569.16	£435.89	£450.03	£613.10	£124.64	£378.20	£4863.72

FEC100-Pw, fluorouracil, epirubicin, cyclophosphamide and weekly paclitaxel; FEC100-T, fluorouracil, epirubicin, cyclophosphamide and docetaxel; FEC75, fluorouracil, epirubicin and cyclophosphamide; TC, docetaxel and cyclophosphamide.

**TABLE 87** Endocrine therapy costs applied in the EAG model

Endocrine therapy	Proportion of patients	Dosage (per day)	Product	Price per pack	Annual cost	Source
Tamoxifen	0.40	20 mg	30 × 20-mg tablet (various manufacturers)	£2.88	£35.06	BNF <sup>194</sup>
Anastrozole	0.20	1 mg	28 × 1-mg tablet (various manufacturers)	£1.08 (NHS Drug Tariff price)	£14.09	
Letrozole	0.20	2.5 mg	28 × 2.5-mg tablet (Alliance Healthcare)	£2.52	£32.87	
Exemestane	0.20	25 mg	30 × 25-mg tablet (various manufacturers)	£5.71 (NHS Drug Tariff price)	£69.52	

**TABLE 88** Cusumano *et al.*<sup>167</sup> post-test chemotherapy probabilities (node negative and node positive)

Test risk classification	Post-test chemotherapy probability	
	Node negative	Node positive
Low risk	0.05	0.36
High risk	0.92	0.99

**TABLE 89** Penault-Llorca *et al.*<sup>162</sup> post-test chemotherapy probabilities (LN0)

Test risk classification	Post-test chemotherapy probability
Low risk	0.01
High risk	0.87

**TABLE 90** Baseline probability of chemotherapy adjusted by oncotype DX Breast Recurrence Score<sup>183</sup> (LN0, intermediate clinical risk)

Oncotype DX risk classification	Probability (no test)
Low risk	Confidential information has been removed
Intermediate risk	Confidential information has been removed
High risk	Confidential information has been removed

**TABLE 91** Risk classification probabilities and 10-year DMFI probabilities for RSPC (from TransATAC analysis<sup>46</sup>)

Test risk classification	Classification probability	10-year DMFI
<b>LN0, NPI ≤ 3.4</b>		
Low risk	0.89	0.978
Intermediate risk	0.09	0.839
High risk	0.02	0.635
<b>LN0, NPI &gt; 3.4</b>		
Low risk	0.52	0.858
Intermediate risk	0.30	0.817
High risk	0.18	0.762

**TABLE 92** Prosigna risk classification and distant metastases probabilities derived from Gnant and Filipits<sup>104</sup> (LN+)

Test risk classification	Classification probability	10-year DMFS
Low risk	0.04	1.00
Intermediate risk	0.34	0.94
High risk	0.62	0.76

**TABLE 93** EndoPredict Clinical risk classification and distant metastases probabilities derived from Dubsy *et al.*<sup>120</sup> (LN+)

Test risk classification	Classification probability	10-year DMFS
Low risk	0.24	0.95
High risk	0.76	0.72

**TABLE 94** MammaPrint risk classification and distant metastases probabilities derived from van 't Veer *et al.*<sup>91</sup> (LN0)

Test risk classification	Classification probability	10-year DMFS
Low risk	0.71	0.93
High risk	0.29	0.85



## Appendix 9 External Assessment Group post-test chemotherapy use survey disseminated to UK Breast Cancer Group members

The following questionnaire was circulated via e-mail to members of the UKBCG.

### Questionnaire: Use of adjuvant chemotherapy for breast cancer based on the results of genomic/immunohistochemical tests

A team of researchers at the University of Sheffield is undertaking an assessment of the clinical and cost-effectiveness of alternative risk stratification tests for ER-positive, HER2-negative women with early breast cancer. The cost-effectiveness analysis element of this work requires estimates of the proportion of patients who go on to receive adjuvant chemotherapy based on the results of these tests.

Please consider the following three populations of women with ER-positive, HER2-negative with early breast cancer:

- (1) Node-negative NPI<3.4
- (2) Node-negative NPI>3.4
- (3) Node-positive (1-3 nodes)

Based on your own subjective opinion, please estimate the probability that a woman in each of these subgroups and with each genomic/immunohistochemical test result would go on to receive adjuvant chemotherapy. Please complete both Tables 1 and 2.

**Table 1: Chemotherapy decisions based on risk score for tests which give 3 classifications (e.g. Oncotype DX, Prosigna)**

Risk score	Probability patient with test result would receive chemotherapy		
	(1) Node-negative NPI<3.4	(2) Node-negative NPI>3.4	(3) Node-positive (1-3 nodes)
Low-risk	PLEASE COMPLETE	PLEASE COMPLETE	PLEASE COMPLETE
Intermediate-risk	PLEASE COMPLETE	PLEASE COMPLETE	PLEASE COMPLETE
High-risk	PLEASE COMPLETE	PLEASE COMPLETE	PLEASE COMPLETE

**Table 2: Chemotherapy decisions based on risk score for tests which give 2 classifications (e.g. MammaPrint and EndoPredict)**

Risk score	Probability patient with test result would receive chemotherapy		
	(1) Node-negative NPI<3.4	(2) Node-negative NPI>3.4	(3) Node-positive (1-3 nodes)
Low-risk	PLEASE COMPLETE	PLEASE COMPLETE	PLEASE COMPLETE
High-risk	PLEASE COMPLETE	PLEASE COMPLETE	PLEASE COMPLETE

### Survey results

Eleven oncologists completed the questionnaire. The mean probabilities obtained from the survey are presented in Tables 3 and 4.

**Table 3: Chemotherapy decisions based on risk score for tests which give 3 classifications (e.g. Oncotype DX, Prosigna)**

Risk score	Probability patient with test result would receive chemotherapy		
	(1) Node-negative NPI<3.4	(2) Node-negative NPI>3.4	(3) Node-positive (1-3 nodes)
Low-risk	0%	4%	41%
Intermediate-risk	20%	41%	72%
High-risk	77%	91%	95%

**Table 4: Chemotherapy decisions based on risk score for tests which give 2 classifications (e.g. MammaPrint and EndoPredict)**

Risk score	Probability patient with test result would receive chemotherapy		
	(1) Node-negative NPI<3.4	(2) Node-negative NPI>3.4	(3) Node-positive (1-3 nodes)
Low-risk	1%	14%	36%
High-risk	74%	91%	96%

## Appendix 10 Modelled chemotherapy use with and without tumour profiling tests (External Assessment Group model)

Subgroup	Test	No test	Net change
<b><i>Oncotype DX vs. current practice</i></b>			
LN0 NPI ≤ 3.4	0.076	0.072	0.004
LN0 NPI > 3.4	0.273	0.430	-0.157
LN1-3	0.337	0.627	-0.290
<b><i>IHC4+C vs. current practice</i></b>			
LN0 NPI ≤ 3.4	0.030	0.072	-0.042
LN0 NPI > 3.4	0.355	0.430	-0.075
LN1-3	0.554	0.627	-0.073
<b><i>Prosigna vs. current practice</i></b>			
LN0 NPI ≤ 3.4	0.075	0.072	0.003
LN0 NPI > 3.4	0.435	0.430	0.005
LN1-3	0.709	0.627	0.082
<b><i>EPClin vs. current practice</i></b>			
LN0 NPI ≤ 3.4	0.140	0.072	0.068
LN0 NPI > 3.4	0.438	0.430	0.008
LN1-3	0.603	0.627	-0.024
<b><i>MammaPrint vs. current practice</i></b>			
MINDACT overall population	0.319	0.466	-0.148
mAOL high risk	0.445	0.772	-0.327
mAOL low risk	0.191	0.159	0.033

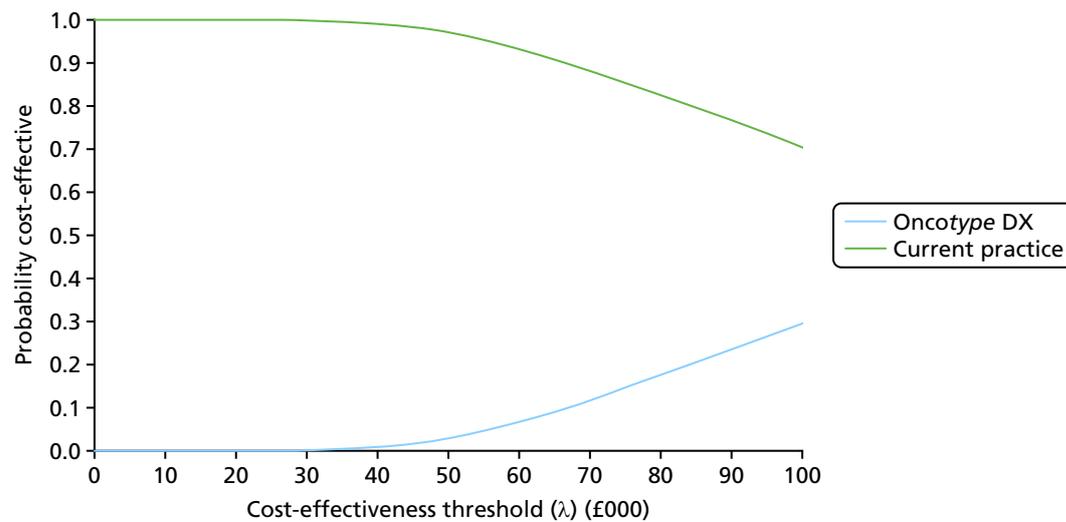


## Appendix 11 External Assessment Group cost-effectiveness acceptability curves

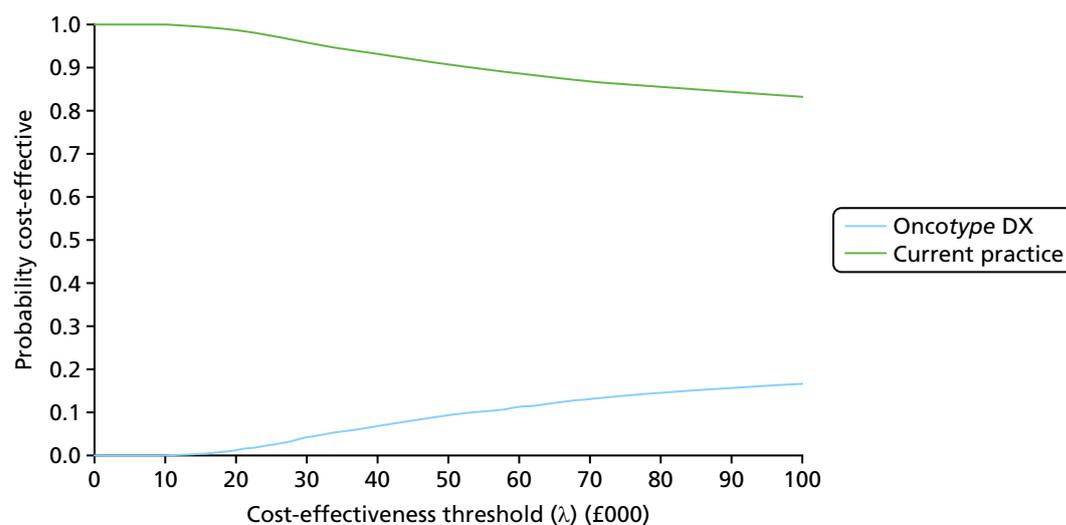
### Cost-effectiveness acceptability curves

#### *Oncotype DX versus current practice*

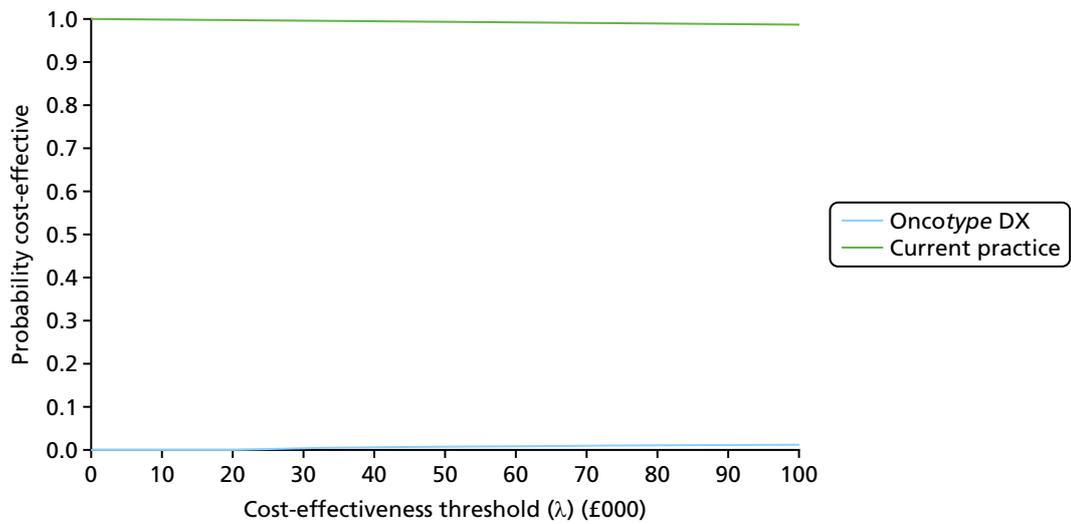
Node-negative Nottingham Prognostic Index score of  $\leq 3.4$



Node-negative Nottingham Prognostic Index score of  $> 3.4$

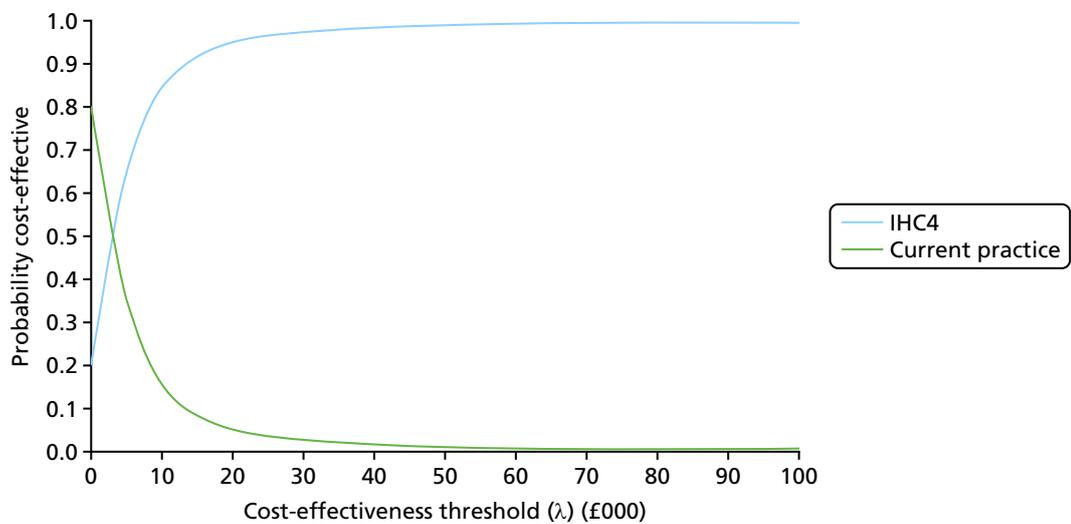


Node positive (one to three nodes)

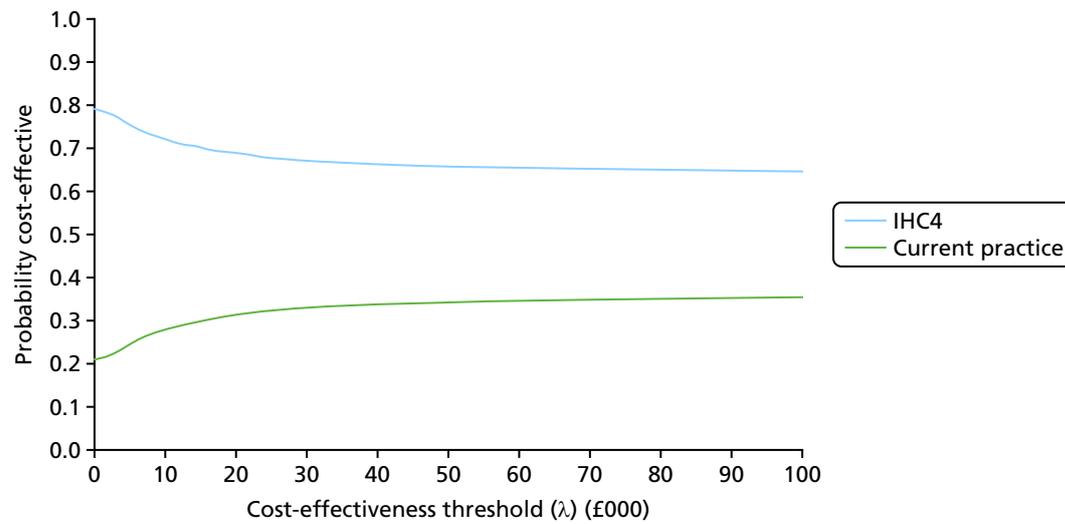


### IHC4+C versus current practice

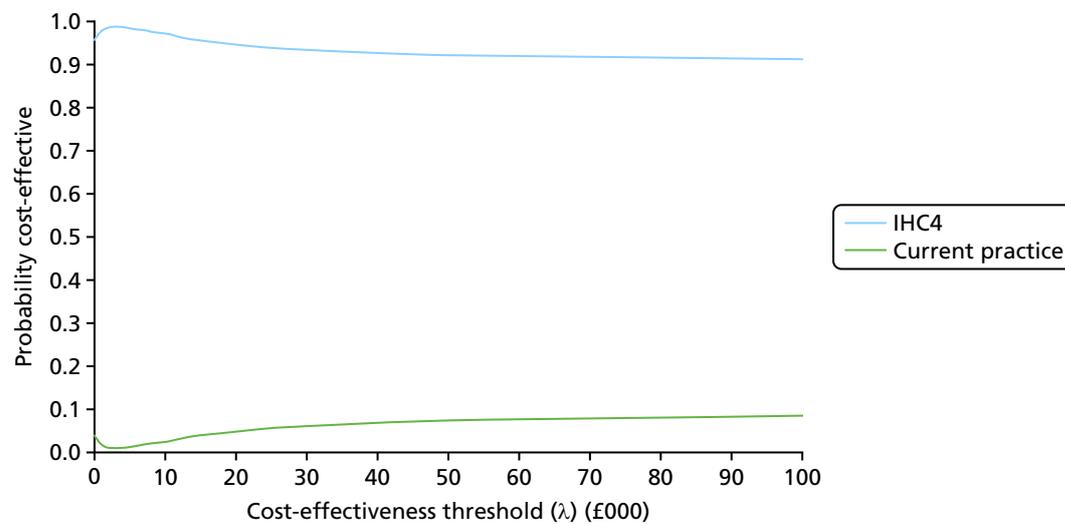
Node-negative Nottingham Prognostic Index score of  $\leq 3.4$

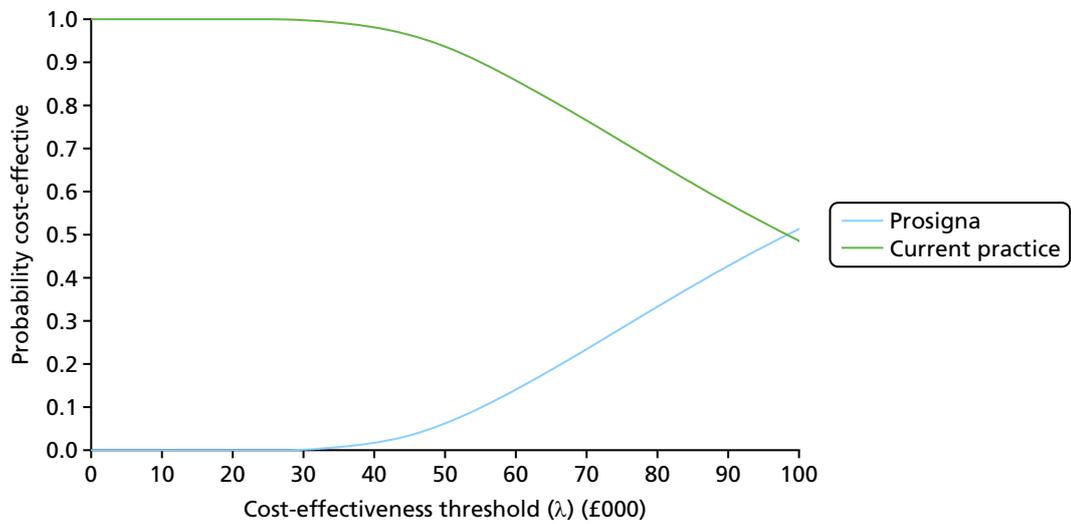
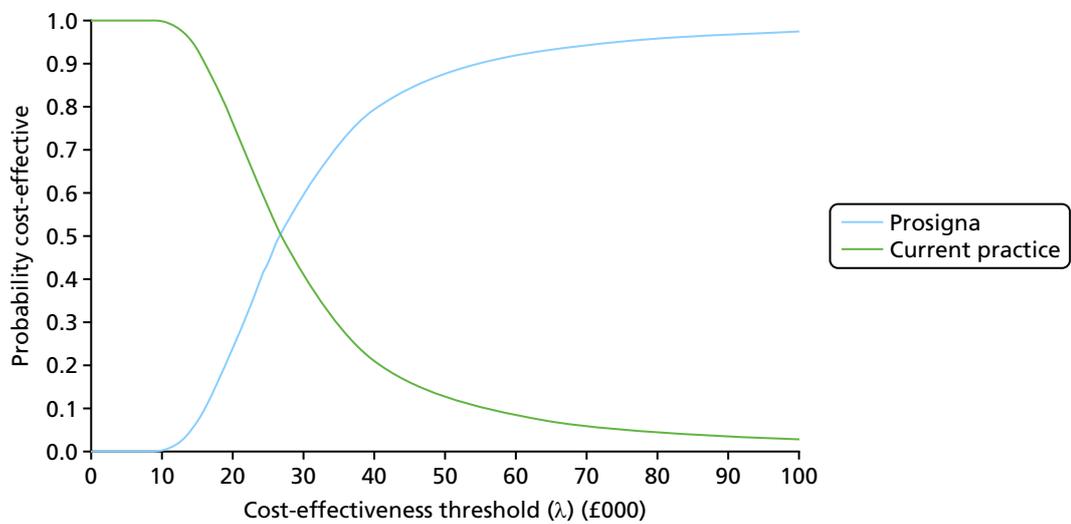


## Node-negative Nottingham Prognostic Index score of &gt; 3.4

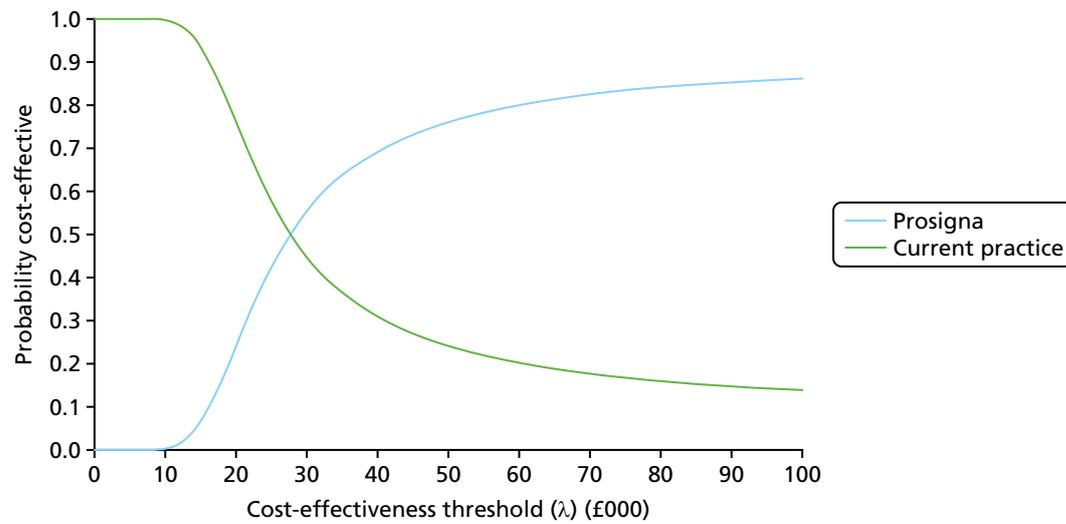
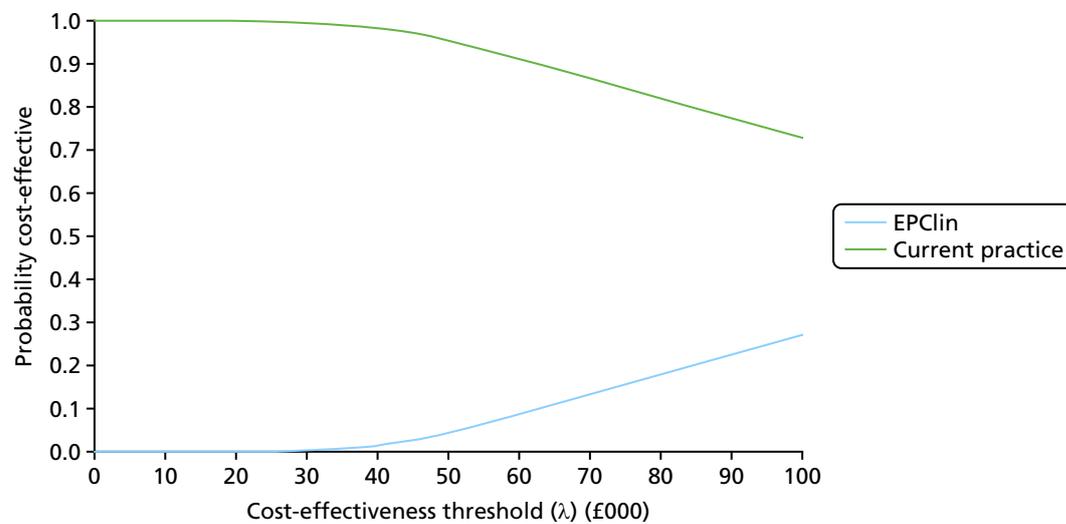


## Node positive (one to three nodes)

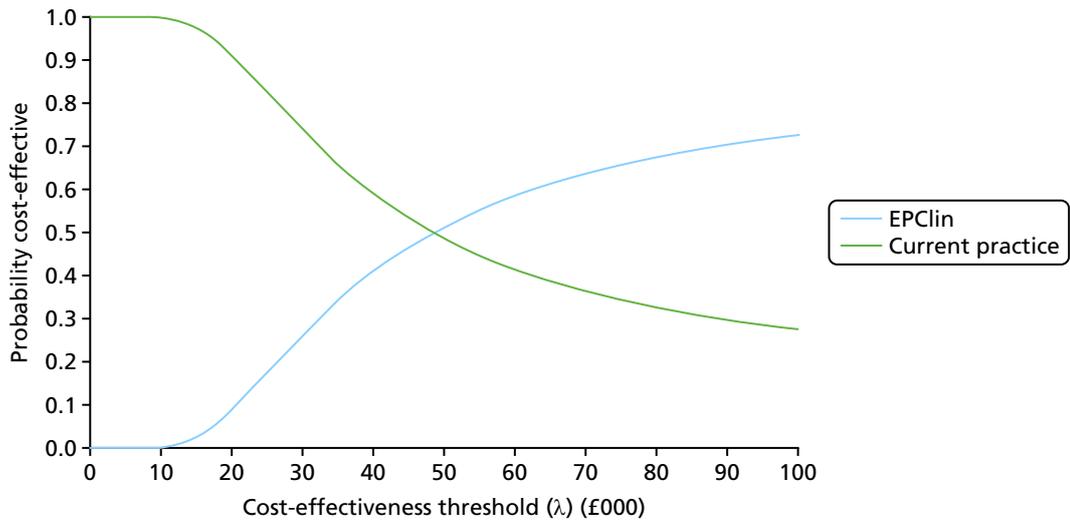


*Prosigna versus current practice*Node-negative Nottingham Prognostic Index score of  $\leq 3.4$ Node-negative Nottingham Prognostic Index score of  $> 3.4$ 

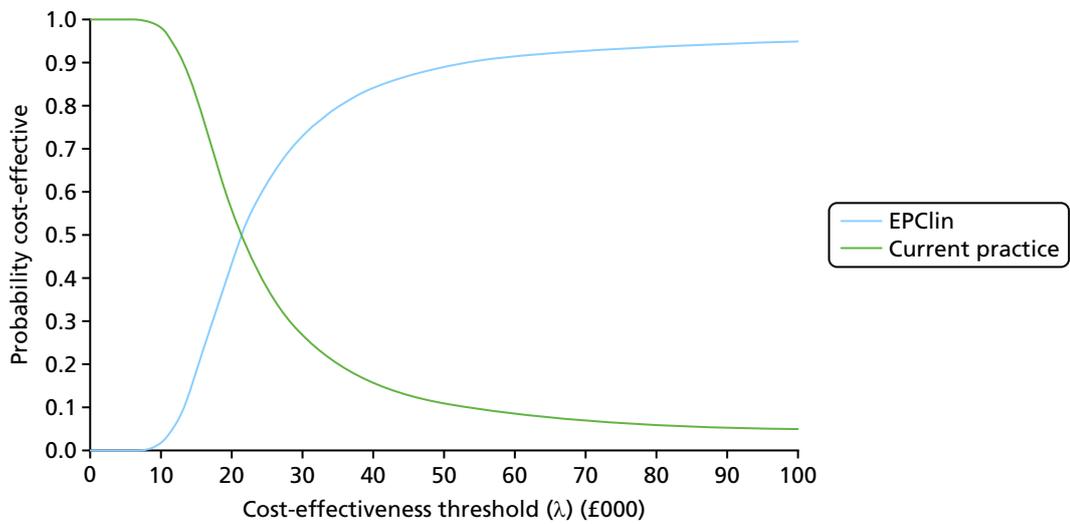
## Node positive (one to three nodes)

*EndoPredict Clinical versus current practice*Node-negative Nottingham Prognostic Index score of  $\leq 3.4$ 

Node-negative Nottingham Prognostic Index score of > 3.4

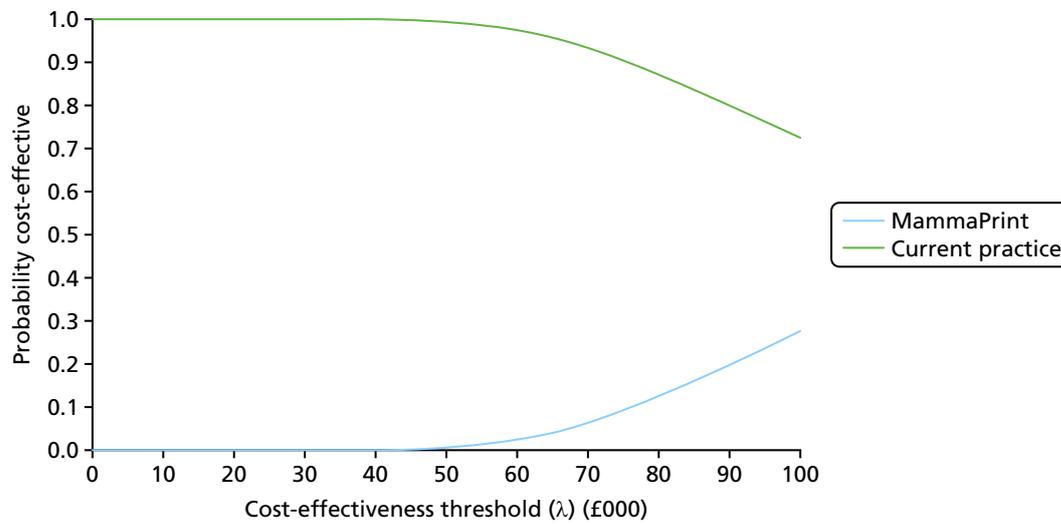


Node positive (one to three nodes)

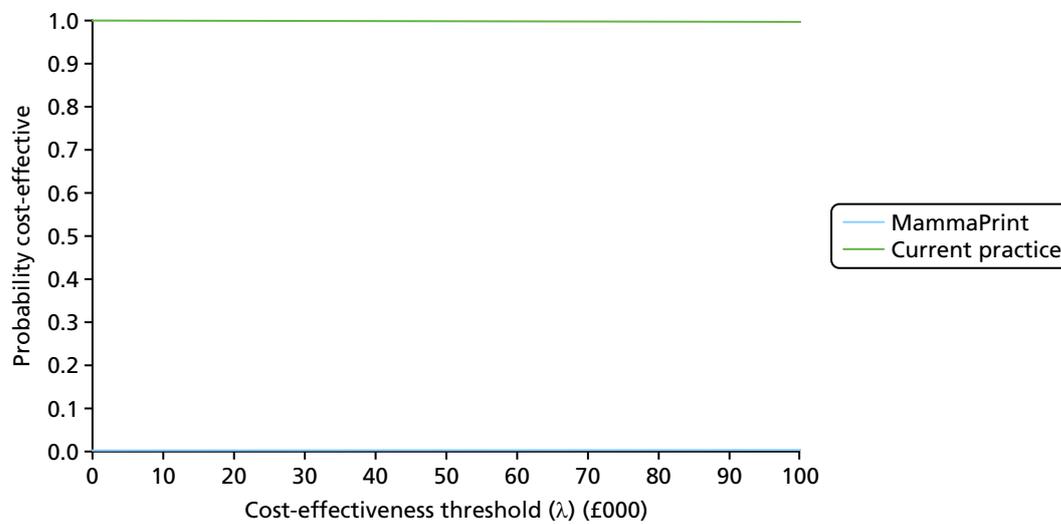


## MammaPrint versus current practice

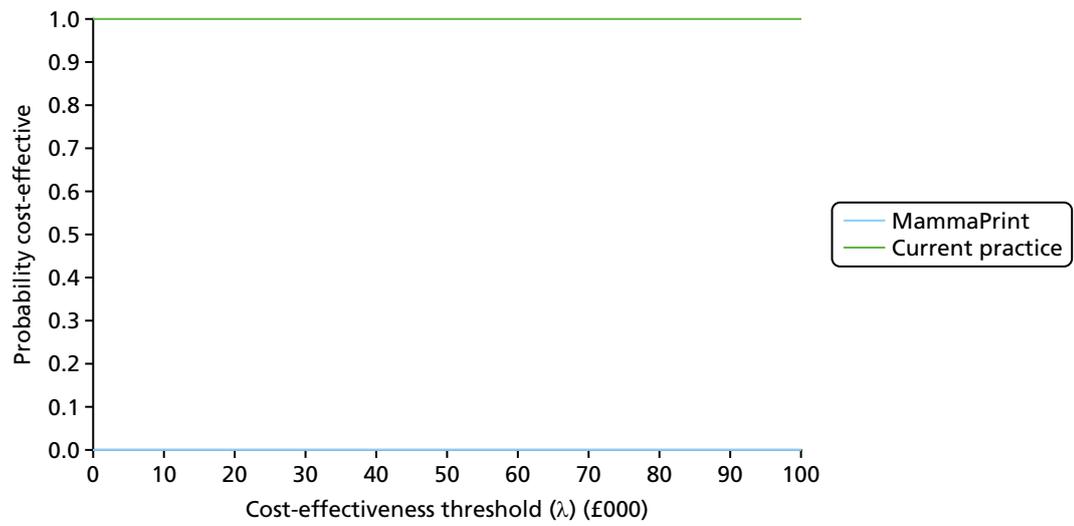
### Overall MINDACT population



### Modified Adjuvant! Online high-risk subgroup



## Modified Adjuvant! Online low-risk subgroup



## Appendix 12 Additional economic analyses undertaken after submission of the original External Assessment Group report

This appendix contains additional economic analyses undertaken after submission of the original EAG report.

### Cost-effectiveness of chemotherapy by risk subgroup

During the consultation on the EAG report and the Diagnostic Consultation Document, it was suggested that the EAG model is predisposed to find giving chemotherapy to all patients a clinically effective and cost-effective use of resources. This interpretation of the model is inaccurate. In the interests of clarity, *Table 95* presents the results of an analysis comparing 100% chemotherapy versus 0% chemotherapy using the EAG model. As shown in the table, the strategy involving the indiscriminate use of chemotherapy is dominated by the no-chemotherapy option for patients with a NPI of  $\leq 3.4$  (i.e. chemotherapy generates fewer QALYs at a greater cost). Chemotherapy appears to have a favourable clinical effectiveness and cost-effectiveness profile within the LN0, NPI > 3.4 and LN+ subgroups.

### Quality-adjusted life-year shortfall analysis to account for missing adverse events

In the light of the uncertainties associated with the analysis presented in *Chapter 3, Independent economic evaluation*, the EAG undertook a further analysis that presents the QALY shortfall associated with each test achieving an ICER of £20,000 and £30,000 per QALY gained, based on the deterministic version of the EAG model (*Tables 96–101*). Other things being equal, this additional analysis may further inform the appraisal committee's deliberations around whether or not other factors that cannot be reliably quantified might have a sufficient impact on the ICERs of the tumour profiling tests to change the interpretation of the model results.

Within each analysis, the QALY shortfall represents the additional number of incremental QALYs that would need to be accrued, given the currently quantified estimates of the incremental QALYs gained for the test and its incremental cost, in order for each test to achieve an ICER at a particular threshold ( $\lambda = £20,000$  per QALY gained or  $\lambda = £30,000$  per QALY gained). In health economic terms, this QALY shortfall is equivalent to net clinical benefit. The NICE Diagnostic Appraisal Committee may find it useful to consider whether the expected magnitude of the health losses avoided by reducing chemotherapy use via tumour profiling tests that are not captured in the EAG model is likely to be equal to or greater than

**TABLE 95** Cost-effectiveness of chemotherapy vs. no chemotherapy

Subgroup	Option	QALYs	Costs	Incremental QALYs	Incremental costs	ICER
LN0, NPI $\leq 3.4$	100% chemotherapy	13.83	£7454	-0.04	£3670	Dominated
	No chemotherapy	13.87	£3784	-	-	-
LN0, NPI > 3.4	100% chemotherapy	12.85	£11,700	0.27	£2316	£8449
	No chemotherapy	12.58	£9384	-	-	-
LN+	100% chemotherapy	12.63	£12,668	0.35	£2011	£5787
	No chemotherapy	12.28	£10,658	-	-	-

**TABLE 96** The QALY shortfall analysis: oncotype DX (prognostic benefit only)

Oncotype DX (prognostic)	Subgroup		
	LN0, NPI < 3.4	LN0, NPI > 3.4	LN1-3
Incremental QALYs	0.01	-0.02	-0.07
Incremental costs	£1317	£869	£647
ICER	£120,144	Dominated	Dominated
QALY shortfall to achieve ICER of £20,000/QALY gained	0.05	0.06	0.10
QALY shortfall to achieve ICER of £30,000/QALY gained	0.03	0.04	0.09
Proportion of patients avoiding chemotherapy owing to testing	0.00	0.16	0.29
Proportion of patients with unaccounted AEs (assumption based on consultation responses)	0.25	0.25	0.25
Proportion of patients tested avoiding chemotherapy with unaccounted AEs	N/A – more get chemotherapy in test group	0.04	0.07
QALY loss for patients avoiding chemotherapy with unaccounted AEs required to achieve shortfall at $\lambda = £20,000/QALY$	N/A – more get chemotherapy in test group	1.49	1.44
QALY loss for patients avoiding chemotherapy with unaccounted AEs required to achieve shortfall at $\lambda = £30,000/QALY$	N/A – more get chemotherapy in test group	1.12	1.29
N/A, not applicable.			

**TABLE 97** The QALY shortfall analysis: oncotype DX (predictive benefit)

Oncotype DX (predictive)	Subgroup		
	LN0, NPI < 3.4	LN0, NPI > 3.4	LN1-3
Incremental QALYs	0.04	0.27	0.09
Incremental costs	£1211	-£364	-£68
ICER	£34,245	Dominating	Dominating
QALY shortfall to achieve ICER of £20,000/QALY gained	0.03	N/A – ICER already below threshold	N/A – ICER already below threshold
QALY shortfall to achieve ICER of £30,000/QALY gained	0.01	N/A – ICER already below threshold	N/A – ICER already below threshold
Proportion of patients avoiding chemotherapy owing to testing	0.00	0.16	0.29
Proportion of patients with unaccounted AEs (assumption based on consultation responses)	0.25	0.25	0.25
Proportion of patients tested avoiding chemotherapy with unaccounted AEs	N/A – more get chemotherapy in test group	0.04	0.07

**TABLE 97** The QALY shortfall analysis: oncotype DX (predictive benefit) (*continued*)

Oncotype DX (predictive)	Subgroup		
	LN0, NPI < 3.4	LN0, NPI > 3.4	LN1–3
QALY loss for patients avoiding chemotherapy with unaccounted AEs required to achieve shortfall at $\lambda = \text{£}20,000/\text{QALY}$	N/A – more get chemotherapy in test group	N/A – ICER already below threshold	N/A – ICER already below threshold
QALY loss for patients avoiding chemotherapy with unaccounted AEs required to achieve shortfall at $\lambda = \text{£}30,000/\text{QALY}$	N/A – more get chemotherapy in test group	N/A – ICER already below threshold	N/A – ICER already below threshold
N/A, not applicable.			

**TABLE 98** The QALY shortfall analysis: IHC4+C

IHC4+C	Subgroup		
	LN0, NPI < 3.4	LN0, NPI > 3.4	LN1–3
Incremental QALYs	0.01	0.01	0.05
Incremental costs	£22	–£89	–£269
ICER	£2752	Dominating	Dominating
QALY shortfall to achieve ICER of £20,000/QALY gained	N/A – ICER already below threshold	N/A – ICER already below threshold	N/A – ICER already below threshold
QALY shortfall to achieve ICER of £30,000/QALY gained	N/A – ICER already below threshold	N/A – ICER already below threshold	N/A – ICER already below threshold
Proportion of patients avoiding chemotherapy owing to testing	0.04	0.08	0.07
Proportion of patients with unaccounted AEs (assumption based on consultation responses)	0.25	0.25	0.25
Proportion of patients tested avoiding chemotherapy with unaccounted AEs	0.01	0.02	0.02
QALY loss for patients avoiding chemotherapy with unaccounted AEs required to achieve shortfall at $\lambda = \text{£}20,000/\text{QALY}$	N/A – ICER already below threshold	N/A – ICER already below threshold	N/A – ICER already below threshold
QALY loss for patients avoiding chemotherapy with unaccounted AEs required to achieve shortfall at $\lambda = \text{£}30,000/\text{QALY}$	N/A – ICER already below threshold	N/A – ICER already below threshold	N/A – ICER already below threshold
N/A, not applicable.			

TABLE 99 The QALY shortfall analysis: Prosigna

Prosigna	Subgroup		
	LN0, NPI < 3.4	LN0, NPI > 3.4	LN1-3
Incremental QALYs	0.02	0.07	0.07
Incremental costs	£1891	£1713	£1967
ICER	£89,693	£25,857	£28,666
QALY shortfall to achieve ICER of £20,000/QALY gained	0.07	0.02	0.03
QALY shortfall to achieve ICER of £30,000/QALY gained	0.04	N/A – ICER already below threshold	N/A – ICER already below threshold
Proportion of patients avoiding chemotherapy owing to testing	0.00	-0.01	-0.08
Proportion of patients with unaccounted AEs (assumption based on consultation responses)	0.25	0.25	0.25
Proportion of patients tested avoiding chemotherapy with unaccounted AEs	N/A – more get chemotherapy in test group	N/A – more get chemotherapy in test group	N/A – more get chemotherapy in test group
QALY loss for patients avoiding chemotherapy with unaccounted AEs required to achieve shortfall at $\lambda = £20,000/QALY$	N/A – more get chemotherapy in test group	N/A – more get chemotherapy in test group	N/A – more get chemotherapy in test group
QALY loss for patients avoiding chemotherapy with unaccounted AEs required to achieve shortfall at $\lambda = £30,000/QALY$	N/A – more get chemotherapy in test group	N/A – more get chemotherapy in test group	N/A – more get chemotherapy in test group

N/A, not applicable.

TABLE 100 The QALY shortfall analysis: EPclin

EPclin	Subgroup		
	LN0, NPI < 3.4	LN0, NPI > 3.4	LN1-3
Incremental QALYs	0.01	0.03	0.06
Incremental costs	£1686	£1401	£1185
ICER	£141,848	£46,482	£21,489
QALY shortfall to achieve ICER of £20,000/QALY gained	0.07	0.04	0.00
QALY shortfall to achieve ICER of £30,000/QALY gained	0.04	0.02	N/A – ICER already below threshold
Proportion of patients avoiding chemotherapy owing to testing	-0.07	-0.01	0.02
Proportion of patients with unaccounted AEs (assumption based on consultation responses)	0.25	0.25	0.25
Proportion of patients tested avoiding chemotherapy with unaccounted AEs	N/A – more get chemotherapy in test group	N/A – more get chemotherapy in test group	0.01
QALY loss for patients avoiding chemotherapy with unaccounted AEs required to achieve shortfall at $\lambda = £20,000/QALY$	N/A – more get chemotherapy in test group	N/A – more get chemotherapy in test group	0.69
QALY loss for patients avoiding chemotherapy with unaccounted AEs required to achieve shortfall at $\lambda = £30,000/QALY$	N/A – more get chemotherapy in test group	N/A – more get chemotherapy in test group	N/A – ICER already below threshold

N/A, not applicable.

**TABLE 101** The QALY shortfall analysis: MammaPrint

MammaPrint	Subgroup		
	MINDACT ITT	MINDACT high risk	MINDACT low risk
Incremental QALYs	0.01	-0.04	0.01
Incremental costs	£1757	£1380	£2415
ICER	£134,059	Dominated	£399,182
QALY shortfall to achieve ICER of £20,000/QALY gained	0.07	0.11	0.11
QALY shortfall to achieve ICER of £30,000/QALY gained	0.05	0.09	0.07
Proportion of patients avoiding chemotherapy owing to testing	0.15	0.33	-0.03
Proportion of patients with unaccounted AEs (assumption based on consultation responses)	0.25	0.25	0.25
Proportion of patients tested avoiding chemotherapy with unaccounted AEs	0.04	0.08	N/A – more get chemotherapy in test group
QALY loss for patients avoiding chemotherapy with unaccounted AEs required to achieve shortfall at $\lambda = £20,000/QALY$	2.03	1.39	N/A – more get chemotherapy in test group
QALY loss for patients avoiding chemotherapy with unaccounted AEs required to achieve shortfall at $\lambda = £30,000/QALY$	1.23	1.11	N/A – more get chemotherapy in test group

N/A, not applicable.

this estimated QALY shortfall. It should be noted that this analysis is predicated on the commentators' assumption that the adverse effects of chemotherapy have been underestimated in the EAG's model. However, the EAG model suggests that with the exception of IHC4+C, all tests increase chemotherapy use in at least some subgroups (see *Appendix 10*); where this is the case, changing the balance of the net health gains and losses of chemotherapy will produce less favourable ICERs for the tumour profiling tests. It should also be noted that any potential underestimation of QALY losses only apply to those patients who would have received chemotherapy and who would have experienced associated late effects who now do not receive chemotherapy owing to the tumour profiling test result and thus avoid these late effects.

The QALY shortfall analysis operates as follows. As shown in *Table 96*, within the LN0 NPI > 3.4 group, oncotype DX (assuming prognostic benefit only) is estimated to lead to -0.02 QALYs and additional costs of £869 compared with no testing, hence it is expected to be dominated by no testing. In this subgroup, oncotype DX would need to make up a further 0.06 QALYs in order to achieve an ICER of £20,000 per QALY gained given its incremental cost [ $£869/(0.06 + -0.02) = £20,000$ ]. Within this subgroup, the EAG model suggests that the probability of receiving chemotherapy is reduced by 16% owing to the use of oncotype DX. Assuming that 25% of these patients experience late effects of chemotherapy that are not accounted for within the EAG model, this means that 4% ( $0.16 \times 0.25$ ) of those forgoing chemotherapy will avoid late effects. The overall QALY shortfall of 0.06 QALYs and the probability of avoiding late effects of 0.04 means that each patient who would have experienced a late effect of chemotherapy would have had to have lost 1.49 QALYs ( $0.06/0.04$ ) due to that AE in order for oncotype DX to be cost-effective at a threshold of £20,000 per QALY gained.

The results for this analysis are summarised in the following sections.

**Oncotype DX (prognostic benefit assumed) (see Table 96)**

- For the LN0, NPI  $\leq$  3.4 subgroup, the analysis is not relevant as more patients receive chemotherapy in the test group.
- For the LN0, NPI  $>$  3.4 subgroup, each patient who avoids chemotherapy and avoids experiencing a late AE not quantified in the EAG model would have to save 1.49 QALYs due to the unquantified AE in order for oncotype DX to have an ICER of £20,000 per QALY gained. Assuming a threshold of £30,000 per QALY gained, the equivalent value is 1.12 QALYs per patient.
- In the LN1–3 subgroup, each patient who avoids chemotherapy and avoids experiencing a late AE not quantified in the EAG model would have to save 1.44 QALYs due to the unquantified AE in order for oncotype DX to have an ICER of £20,000 per QALY gained. Assuming a threshold of £30,000 per QALY gained, the equivalent value is 1.29 QALYs per patient.

**Oncotype DX (predictive benefit assumed) (see Table 97)**

- In the LN0, NPI  $\leq$  3.4 subgroup, the analysis is not relevant as more patients receive chemotherapy in the test group.
- In the LN0, NPI  $>$  3.4 subgroup, the analysis is not relevant as the test dominates.
- In the LN1–3 subgroup, the analysis is not relevant as the test dominates.

**IHC4+C (see Table 98)**

- In the LN0, NPI  $\leq$  3.4 subgroup, the analysis is not relevant as the ICER is already below £20,000 per QALY gained.
- In the LN0, NPI  $>$  3.4 subgroup, the analysis is not relevant as the test dominates.
- In the LN1–3 subgroup, the analysis is not relevant as the test dominates.

**Prosigna (see Table 99)**

- In the LN0, NPI  $\leq$  3.4 subgroup, the analysis is not relevant as the test increases chemotherapy use.
- In the LN0, NPI  $>$  3.4 subgroup, the analysis is not relevant as the test increases chemotherapy use.
- In the LN1–3 subgroup, the analysis is not relevant as the test increases chemotherapy use.

**EndoPredict Clinical (see Table 100)**

- In the LN0, NPI  $\leq$  3.4 subgroup, the analysis is not relevant as the test increases chemotherapy use.
- In the LN0, NPI  $>$  3.4 subgroup, the analysis is not relevant as the test increases chemotherapy use.
- In the LN1–3 subgroup, the analysis is not relevant at a threshold of £30,000 per QALY gained as the ICER is below this. Each patient who avoids chemotherapy and avoids experiencing a late AE not quantified in the EAG model would have to save 0.69 QALYs due to the unquantified AE in order for EPclin to have an ICER of £20,000 per QALY gained.

**MammaPrint (see Table 101)**

- In the MINDACT ITT subgroup, each patient who avoids chemotherapy and avoids experiencing a late AE not quantified in the EAG model would have to save 2.03 QALYs due to the unquantified AE in order for MammaPrint DX to have an ICER of £20,000 per QALY gained. Assuming a threshold of £30,000 per QALY gained, the equivalent value is 1.23 QALYs per patient.
- In the MINDACT high-risk subgroup, each patient who avoids chemotherapy and avoids experiencing a late AE not quantified in the EAG model would have to save 1.39 QALYs due to the unquantified AE in order for MammaPrint to have an ICER of £20,000 per QALY gained. Assuming a threshold of £30,000 per QALY gained, the equivalent value is 1.11 QALYs per patient.
- In the MINDACT low-risk subgroup, the analysis is not relevant as the test increases chemotherapy use.

## Additional analyses of oncotype DX versus usual practice including chemotherapy benefit based on naive indirect comparisons of Study B20, Study B14 and TransATAC: lymph node-negative, Nottingham Prognostic Index > 3.4 subgroup

Table 102 presents estimated HRs for chemotherapy versus no chemotherapy based on naive indirect comparisons of Study B20,<sup>50</sup> Study B14<sup>49</sup> and TransATAC.<sup>46</sup>

Table 103 presents additional economic comparisons of oncotype DX versus usual practice including chemotherapy benefit based on naive indirect comparisons of Study B20,<sup>50</sup> B14<sup>49</sup> and TransATAC.<sup>46</sup> In each analysis, the modelled HR was calibrated against the estimates presented in Table 102. All analyses are based on the deterministic version of the EAG model.

**TABLE 102** Hazard ratios for chemotherapy benefit by oncotype DX risk score based on naive indirect comparisons of Study B20, Study B14 and TransATAC

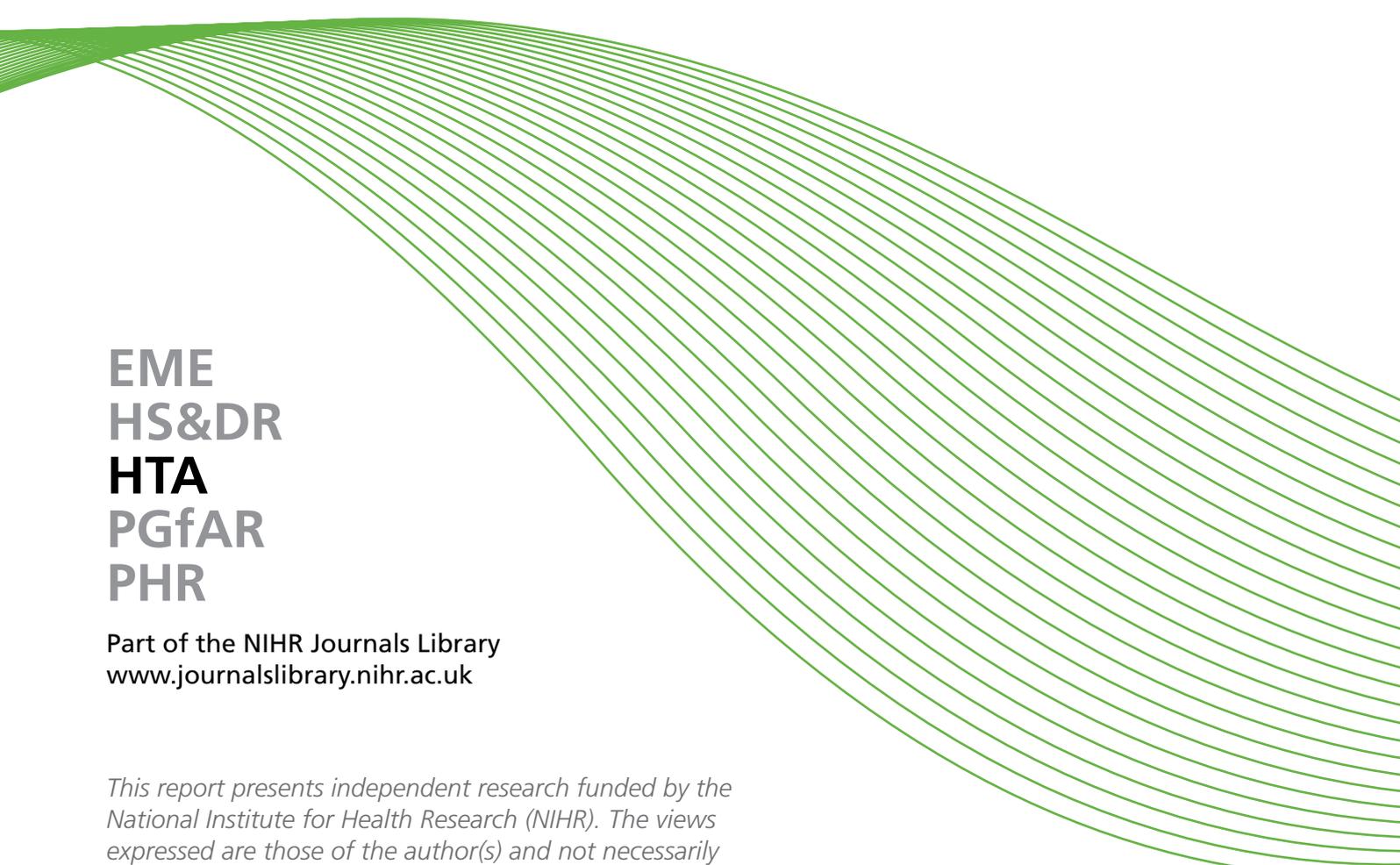
Oncotype DX risk group	10-year DMFS		Estimated HR
	No chemotherapy (%)	Chemotherapy (%)	
<b>B20 vs. B14</b>			
Low	93.20	95.60	0.64
Intermediate	85.70	89.10	0.75
High	69.50	88.10	0.35
<b>B20 vs. TransATAC</b>			
Low	94.90	95.60	0.86
Intermediate	87.70	89.10	0.88
High	77.20	88.10	0.49

**TABLE 103** Additional analyses of oncotype DX vs. usual practice including chemotherapy benefit based on naive indirect comparisons of Study B20, B14 and TransATAC: LN0, NPI > 3.4 subgroup

Option	QALYs	Costs	Incremental QALYs	Incremental costs	ICER (per QALY gained)
<b>Chemotherapy benefit based on indirect comparison of B20 and B14</b>					
Oncotype DX	12.82	£10,664	0.03	£682	£24,334
No test	12.79	£9981	–	–	–
<b>Chemotherapy benefit based on indirect comparison of B20 and TransATAC</b>					
Oncotype DX	12.74	£10,989	0.06	£525	£8150
No test	12.68	£10,465	–	–	–





A decorative graphic consisting of numerous thin, parallel green lines that curve from the left side of the page towards the right, creating a sense of movement and depth.

**EME  
HS&DR  
HTA  
PGfAR  
PHR**

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