**Using cost-effectiveness analysis to quantify the value of genomic-based diagnostic tests: recommendations for practice and research**

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**Running Title:** Quantifying the value of genomic-based diagnostic tests

# Abstract

Aims: New sequencing technologies allow increased opportunities to use genomic-based diagnostic tests (‘genomic-tests’) in routine clinical practice, which will impact healthcare budgets and patients’ outcomes. This paper aims to generate a list of recommendations on how the principles and methods of cost-effectiveness analysis (CEA) can be used to quantify the costs and benefits of genomic-tests.

Methods: A systematic literature search identified publications describing the use of CEA to evaluate genomic-tests. Data were extracted as key concepts to produce a thematic list of previously described challenges and solutions to using CEA to evaluate genomic-tests. Defining features of evaluating genomic-tests were categorized into a list of key recommendations for applying methods in practice and for research needs.

Results: Features producing challenges in the implementation of CEA to evaluate genomic- tests were:  the ability of the tests to diagnose multiple-disorders; potential consequences for future generations suggesting an infinite time-horizon; and the potential need to consider non-health benefits.

Conclusions: CEA was identified as an appropriate evaluative framework for genomic-tests, although standard methods may need modification and important methods research questions remain. Key recommendations suggest a need for research to value: sharing genomic information across generations; genomic-tests for multiple disorders; and health and non-health benefits.

# Introduction

New technologies, such as next generation sequencing and whole genomic sequencing, are developing rapidly. These new technologies have the potential to offer more patients a genomic-based diagnosis for their inherited condition while also moving the test to the front of the diagnostic pathway. Increased opportunities to use genomic-based diagnostic tests (hereafter called ‘genomic-tests’) will inevitably have an impact on healthcare budgets and health outcomes.

Healthcare systems face budgetary constraints and any new, more costly service provided by the health system must necessarily imply either disinvestment or limits on opportunities to invest in other areas of care. This results in opportunity costs in the form of forgone health gains to other patients. Cost-effectiveness analysis (CEA) is used to inform resource allocation decisions by i) determining the health consequences of alternative interventions and programmes; ii) assessing the costs to the healthcare system; and iii) determining whether the new intervention is good value compared with how the resources could be used elsewhere in the healthcare system by assessing the opportunity costs, generally using a cost-effectiveness threshold (Claxton et al., 2015). In England, the use of CEA is well established for the consideration of investment in new technologies through the National Institute for Health and Care Excellence’s (NICE) technology appraisal (NICE, 2013) and diagnostic assessment programme (NICE, 2012).

Historically, the assessment of tests to provide a genetic diagnosis has been the remit of the UK Genetic Testing Network (UKGTN). The UKGTN has developed a ‘Gene Dossier’ process to evaluate tests before they can be recommended for use in clinical practice on a national level (Kroese et al., 2007). Laboratories are required to submit evidence on the analytical validity, clinical validity, clinical utility, ethical implications and the estimated cost of the test, but do not require the same level of economic evidence that NICE uses in its appraisal programmes (Payne, 2009). In the future, the UKGTN may broaden its remit to consider the cost-effectiveness of new tests or NICE may take on a new remit to appraise genomic-tests. If this were to happen then it is necessary to understand how CEA can be applied to genomic-tests (Payne et al., 2013; Payne and Shabaruddin, 2010).

This paper aims to generate a list of recommendations on if, and how, the principles and methods of CEA can be used to quantify the incremental costs and benefits of genomic-tests.

# methods

A systematic review, conducted February 2016 in accordance with published recommendations, identified articles that have focused on the key methods challenges, and potential solutions, associated with the economic evaluation of genomic-tests. A bidirectional citation searching technique was used to identify relevant papers (Hinde and Spackman, 2014). This involves identifying an initial set of relevant studies, which are then used to identify additional literature by searching their references and citations. This process is repeated until no new papers of relevance are discovered. The initial studies were identified in consultation with other researchers working in this area, and are listed in Appendix 1.

Papers were excluded if they did not contain some reference to methods challenges associated with the economic evaluation of genomic-tests, either by identifying issues or offering potential solutions to existing ones. To be inclusive, this review took a broad definition of a genomic-test including any study that referred to any type of genetic or genomic data to produce a screening, diagnostic or companion-diagnostic test. Two reviewers read and summarized the final set of papers. Data were extracted as key concepts to produce a thematic list of challenges and solutions to using CEA of genomic-based diagnostic tests. Key recommendations were identified, underpinned by economic theory and methods.

# Results

The literature review identified 2,527 citations and references (Figure 1). A total of 65 papers were considered appropriate for full review (Table 1). Overall, the identified literature suggested that the evaluative framework underpinning cost-effectiveness analysis was appropriate to evaluate genomic-tests. There are some methodological and practical issues that need careful consideration for the design and conduct of CEA. Five key concepts, were identified: role of the intervention; perspective; time horizon; assessment of benefits; and assessment of costs. Within these concepts, two defining features influencing the use of CEA to evaluate genomic- tests were:  the ability of the tests to diagnose multiple-disorders and the potential consequences for future generations. The potential need to consider non-health benefits was a common feature, although not unique to genomic-tests. The key concepts and defining features are now described in detail.

## THE INTERVENTION

To conduct a CEA it is necessary to be clear about the relevant study population, comparators and the nature of the intervention being evaluated. A population may be characterized based on responses to previous diagnostic tests, symptoms, and possibly responses to previous genomic-tests undertaken by family relations. Different types of patients will have different expected outcomes and the cost-effectiveness of the genomic-test will likely be different depending on the patients’ initial characterization. So clearly identifying the population of interest is important as with other types of technology appraisals. Once the patient population has been characterized then it will be possible to determine the other treatments or testing strategies that should be compared with the genomic-test. As with all diagnostics, choosing comparators can be complicated as the number of possible strategies is increased by different test sequences, and the frequency and timing of follow-up.

To appropriately evaluate a genomic-test it is important to clearly define the intervention. Genomic-tests can identify the presence of more than one, and potentially many, clinically relevant disorders. Incidental findings refer to the possibility of finding potential abnormalities that are unrelated to the clinical question for which the test was initiated (Hehir-Kwa et al., 2015). The review found no literature directly considering the evaluation of tests that identify multiple disorders or incidental findings. However, discussions in the current literature suggest that the design and conduct of a CEA of a genomic-test that identifies multiple mutations in causative genes and/or incidental findings will require a different approach to CEA compared to identifying a single gene at a time.

To fulfill the underlying principles of CEA (Drummond et al., 2005), the consequences of all findings from a genomic-test should be included in the analysis. To do this, the goal of the genomic-test must be explicit. The consequences of identifying mutations in multiple causative genes and/or incidental findings will be determined by the clinical judgments made on the basis of the result. If clinical practice is to ignore the additional findings then there is no need to include them in the economic evaluation. If clinical practice is to follow-up on some or all of the findings, incurring resource costs and potential therapeutic decisions with consequences for patients, then this should be reflected in the economic evaluation. In practice, incidental findings has generated the introduction of multidisciplinary team meetings to reach a collective decision on what test result should be reported (Oxford Biomedical Research Centre, 2016). The resources associated with forming these teams need to be accounted for in the costs of the genomic-test.

Researchers could specify the decision problem as a single disorder and then consider each additional disorder iteratively, as is commonly done for the assessment of other types of diagnostic tests. It is important to note that the cost-effectiveness of testing for one disorder, does not guarantee the cost-effectiveness of the test for other disorders, as the identification of additional disorders may be associated with significant cost implications and/or effects on clinical decision making and subsequent (dis)benefits. Alternatively researchers could conduct an economic evaluation for multiple disorders that could be investigated using the same genetic test. Under such an approach, each disorder, within the set to be evaluated, would have the incremental costs and benefits estimated. The incremental costs and benefits from each disorder would be aggregated along with the cost of undertaking the genomic-test and used to estimate the joint cost-effectiveness of the test for the full set of disorders.

Whether iterative or aggregate approaches are taken, a full economic analysis of each disorder being tested is required before a decision can be made about the cost-effectiveness of the test for a particular disorder. These evaluative approaches are likely to be costly, time consuming and require a large amount of evidence and may reach the same decision as a more pragmatic approach. Under a pragmatic approach, an *a priori* judgment could be made as to which disorders are expected to be associated with the greatest effect on clinical decision making, and full economic evaluations only applied to these areas. This approach is likely to restrict the economic evaluation and therefore reimbursement to those disorders for which a treatment is available.

## Perspective

The perspective taken in most economic evaluations is that of the health system or payer (Drummond et al., 2005). Under a healthcare perspective the presumption is that the decision maker is seeking to maximize population health subject to relevant constraints faced by the heath sector. Under the healthcare perspective additional costs such as those falling on carers, employers or other public sectors are not included, and generally the focus is on health-related outcomes (Claxton et al., 2010).

The nature of genomic-tests means that testing may result in health and non-health benefits to the proband (the individual being tested) and all their genetic relations. The information provided by these tests may affect not only their health but, potentially, many other aspects of their lives, for example employment or reproductive decisions. Many authors have argued that economic models need to recognize benefits other than the health effects on the tested individual,(Edwards, 2001; Garrison and Austin, 2007; Hall et al., 1998; Foster et al., 2009; Caughey, 2005; Basu and Meltzer, 2005) and others call for models to include the implication of the genomic-test information on birth decisions, insurance discrimination and privacy (Col, 2003). However, given the remit and financial constraints of health systems, economic evaluations for new health technologies generally focus only on the implications to population health by limiting the perspective of the analysis to capture health benefits alone (NICE, 2013).

In principle, however, economic evaluations can incorporate a broader array of costs and outcomes. When an attempt is made to include all relevant effects (costs and outcomes), a study is often defined as having a ‘societal’ perspective. This would include, for example, changes in productivity, out of pocket transportation costs to patients attending clinics, additional costs and consequences associated with other public sector budgets such as criminal justice or education. It is important to note that any analysis seeking to take such a societal perspective must not only consider the wider costs and benefits of the new activity, but also the wider costs and benefits of comparators and any interventions and services that might be displaced if the new activity incurs additional costs (Claxton et al., 2010). Using a societal perspective can be difficult because trading population health against other outcomes such as educational benefits is likely to be challenging for decision makers and practitioners who are held accountable to the outcomes they achieve in health care. This challenge is partly due to the lack of consensus about how to define and trade-off social goals. Further research is required in appropriate methods for economic evaluation to inform decisions relating to a wider array of costs and outcomes. This research is required not only in the area of genomic-tests but for all medical technologies as the principles of a broader perspective should be applied consistently across all evaluations.

Much of the cost-effectiveness literature on the evaluation of existing genomic-based tests takes a healthcare perspective or does not state the perspective used (Assasi et al., 2012; Djalalov et al., 2011; Rogowski, 2006). Previous literature has called for evaluations to consider a wider perspective to provide the most information to the decision maker and to be clear about what costs and outcomes have been included (Buchanan et al., 2013). However, while a clear statement of the type of perspective being taken is a prerequisite for a robust CEA, further research is needed to decide if, and how, broader perspectives can be implemented.

## time horizons

When determining the time horizon and discount rates for the analysis of a genomic-test, the same principles should be followed as with other types of treatments. Genomic-tests are slightly different from other technologies in that the tests for hereditary diseases may provide benefits and costs to the genetic family for many years. Following the principle that the time horizon should cover all downstream costs and effects of treatments over the period for which differences are expected may justify a very long time horizon. Long-term costs include the cost of storing and sharing genomic information. In the NHS, the 100,000 Genomes Project will adopt a dynamic reporting system which aims to report back to clinicians at least every year (Genomics England, 2017). Currently no national infrastructure is available in the NHS for this type of storage and sharing, so the analyst will have to consider the probability that this information would be passed along or used in the future if the patient is responsible for sharing this information. Alternatively, the analyst could include the costs of implementing storage and sharing. This would require consideration of the costs of keeping it secure and the potential costs of data breaches or misuse. The analyst must also consider the long-term consequences of the future use of the genomic information.

As with public health initiatives and screening technologies, the expected benefits of genomic-tests may occur well into the future. To consider future costs and benefits appropriately, the trade-offs between present and future need to be understood. The UK Treasury recommends that future costs and benefits of public sector goods are discounted at an annual rate of 3.5%.(HM Treasury, 2003) When discounting is applied, the very long-term differences will be minimal and at some time point will no longer affect the cost-effectiveness decision. It would be appropriate for the analyst to report the time horizon at which additional modelling no longer affects the decision and the direction of effect of increasing the time horizon.

## Assessment of benefits

Once the evaluative perspective has been chosen, the appropriate consequences of the test under consideration must be measured and incorporated. Themes identified in the literature were the difficulties associated with capturing the health and non-health consequences of a test to diagnose genetic conditions. Technology assessment (NICE, 2013) and diagnostic assessment (NICE, 2012) methods guides recommend that analyses ‘should include all relevant patient outcomes that change in the care pathway as a result of the diagnostic test or sequence of tests’. However, existing evaluations have been poor in including all the effects of treatments on patient outcomes (Cohen et al., 2013).

To undertake a CEA of a genomic-test, evidence is required about the accuracy of the test, as well as information about how different test results affect patient management, and the subsequent effectiveness of the management strategy. The clinical and cost-effectiveness of diagnostic tests rely on the availability of effective treatments following any diagnosis. It is necessary to determine whether an effective treatment exists for the genetic disorder and what potential management or surveillance strategies are possible.

A full evaluation of the consequences associated with a genomic-test will ideally consider the potential treatment implications to the rest of the genetic family including future generations.(Faulkner et al., 2012; Neumann et al., 2012) This depends on whether the genomic-test is focused on an area in which the hereditary nature of the disease and pattern of inheritance is already known. The hereditary nature of a condition may lead to benefits to family members if they seek medical intervention earlier as a result of the diagnosis. While data collection across generations may represent a challenge, by understanding the hereditary nature of a disease it is possible, using economic modelling, to consider the potential consequences of particular genomic information to future generations. An analyst must be clear about what is known regarding existing hereditary patterns of disease and if the new technology could add new knowledge and take account of these issues in the practical application of the CEA.

The potential health consequences across unborn generations are not well discussed in current methods guides for interventions or diagnostic tests (NICE, 2013, 2012). However, some economic evaluations have sought to include future health gains of unborn children (Ades et al., 1999; Mooney and Lange, 1993). The evaluation of pre-natal and pre-implantation genomic-testing, where the proband is yet to be born, is more challenging due to the role of termination as an available option. An important question when determining what types of consequences might be included in an economic evaluation is whether the proband is yet to be born. Table 1 shows a list of recommendations, posed as key questions to be considered when conducting CEA of genomic-based diagnostic tests.

The consequences (positive and negative) of a genomic-test may go beyond direct health benefits (Payne et al., 2013; Murray, 1994; Payne, 2009). Non-health consequences to the patient and their family include the impact on the ability to make an informed decision by the patient and relations, for example, reproductive, lifestyle or career decisions (Payne et al., 2013; Hall et al., 1998; Neumann et al., 2012; Payne, 2009; Fang et al., 2011; Griffith et al., 2004; Khoury et al., 2006) In most instances there will be no quantifiable health effects of a genome-based diagnostic when it is used as a diagnostic tool for rare inherited disorders for which no treatments are available. The diagnosis of the untreatable disorders might still be valuable if the information can help the patient make life plans and therefore might be included in the economic evaluation to justify the cost of the genomic-test. The value of non-health consequences may be completely independent of the health effects of the test,(Neumann et al., 2012) and, as such, may have a large effect on resource allocation if formally considered in decision making. Literature states that there is little evidence that these have been included in existing economic evaluations (Caughey, 2005; Griffith et al., 2004; Grosse et al., 2008; Sullivan et al., 2012).

The consideration of non-health consequences in economic evaluation is associated with some challenges. Many authors have emphasized that existing methods to quantify benefit do not represent an appropriate method for considering non-health consequences (Faulkner et al., 2012; Payne, 2008; Sullivan et al., 2012; Payne and Thompson, 2013). This is not surprising given that the most common measure, the quality-adjusted life-year (QALY), is a measure of health status; however, there is a literature which discusses its characteristics as a broader measure of individual utility (Pliskin et al., 1980). Some have argued for the use of methods such as willingness-to-pay (Grosse et al., 2008), others have recommended the capabilities approach, which would include the valuing the capability of making an informed decision ( Payne et al., 2013). A key principle that has not been fully recognized in the literature is the need for relevant measures of (health or non-health) outcome to be reflected in the benefits of new interventions but also in the benefits forgone (opportunity costs) when additional costs are imposed. This either requires a broad measure of outcome that reflect all relevant health and non-health consequences, or explicit trade-offs to be quantified in terms of distinct outcomes e.g. how much population health should be forgone in order to generate information of non-health value to individuals.

## Assessment of costs

Many existing CEA restrict costs to include the direct costs of genetic testing and any therapeutic or preventative interventions following the test result (Assasi et al., 2012). However, authors have highlighted that the cost of a genomic-test includes more than just the unit costs of the technology and laboratory consumables. Additional costs include, extra clinic visits, the cost of subsequent treatment, genetic counselling and further diagnostics (Veenstra et al., 2000). In addition, Vegter *et al* (Vegter et al., 2008; Vegter et al., 2010) found substantial variation in the costs associated with the same genomic-tests used to target treatments, and Brown *et al* (Brown and Kessler, 1995) have established that there is substantial variation in the cost of screening and subsequent treatment.

The appropriate estimation of costs is primarily not a methodological issue, beyond the establishment of the perspective, but a practical issue. In general, the issues associated with the variation in the costing approaches could be solved by: adherence to the methods proposed in the economic evaluation guidelines, and conducting more research to construct robust cost estimates relevant to genomic-tests (e.g. micro-costing studies). Examples of such estimates elsewhere in the health sector include the British National Formulary (for pharmaceutical product costs), NHS Reference Costs (for NHS activities) and Personal Social Services Research Unit (for social services) (PSSRU, 2011). The fundamental challenge is that, unlike pharmaceuticals, there is currently no national list of available genomic-tests as each laboratory is free to set their own price (or charge) to clinicians requesting the test.

# Discussion

This paper has sought to generate a list of recommendations on how the principles and methods of CEA can be used to quantify the costs and benefits of genomic-tests. This review has generated a theme-based overview of how CEA is currently used to identify the costs and benefits of genomic-tests. From the review, recommendations have been generated on the key practical issues to be considered in undertaking CEA of genomic-tests, together with areas where future research on methods development should best be targeted.

The general view was that the principles of economic evaluation are applicable for the assessment of genomic-tests. There may be some practical difficulties in implementing CEA, although not all are unique to genomic-tests. Many of the challenges of assessing genomic-tests are similar to other diagnostic tests and solutions to some of these problems are well established (NICE, 2012; Schaafsma et al., 2009).

A commonly identified theme in the review was a lack of evidence for the conduct of CEA of genomic-tests. Lack of data occurs in many contexts but does not preclude the need to follow current recommendations on the conduct of a CEA (Drummond et al., 2005). When determining whether to fund additional research for genetics the opportunity costs of gathering additional evidence should be considered. This can be done using value of information methods and has been suggested in the current published literature on personalised medicine (Annemans et al., 2013).

There would ideally be an improvement in the availability of evidence on the costs associated with genomics. National price lists of genomic-test costs, similar to those instituted for other health interventions, would help avoid the currently reported variation in costs.

In moving towards the use of genomic-tests there is also a need to consider capacity issues. Existing methods of CEA do not generally take account of capacity constraints of resources available in the health system (Brennan et al., 2006). By widening the range of conditions to test and expanding patient populations, there is the potential for genomic-tests to have an impact on the capacity of the health system to deliver the required volume of testing and associated service needs. These capacity constraints would make genomic-tests prohibitively expensive to fund, incurring significant opportunity costs. Evaluations that identify and quantify the use of healthcare resources could usefully inform the impact of introducing whole genome sequencing on service capacity in terms of whether current referral pathways and genetic counselling services can meet the demand as more patients and conditions are tested.

A recurring theme identified in this review was the need for further empirical research. Three particular areas were identified (i) if, and how, should we value whether patient populations trade-off health and non-health consequences of tests; (ii) how to assess the value of storing and sharing genomic information and (iii) the development of methods for choosing among multiple disorders for a more pragmatic cost-effectiveness approach.

**Acknowledgements**

Financial support for this study was provided UK Department of Health Policy Research Programme under the Policy Research Unit in Economic Evaluation of Health and Care Interventions. The funding agreement ensured the authors’ independence in designing the study, interpreting the data, and writing and publishing the report. The views expressed in this report are those of the authors and not those of the UK Department of Health. Any errors are the responsibility of the authors.

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