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Guidelines and Recommendations

Evidence-informed recommendations on managing breast screening atypia: perspectives from an expert panel consensus meeting reviewing results from the Sloane atypia project

Karoline Freeman , PhD[1], Alice Mansbridge, BSc[1], Hilary Stobart, MSc[2], Karen Clements, BSc[3], Matthew G. Wallis, MBChB[4], Sarah E. Pinder, MBChB[5], Olive Kearins, MSc[3], Abeer M. Shaaban, MBBCh, MSc, PhD[6], Cliona C. Kirwan, MBBS, BSc, PhD[7], Louise S. Wilkinson, BMBCh[8], Sharon Webb, MPH[9], Emma O'Sullivan, BSc[9], Jacquie Jenkins, MSc[9], Suzanne Wright, PhD[9], Kathryn Taylor, DCR, MSc[4], Claire Bailey, BNurs[10], Chris Holcombe, MD[11], Lynda Wyld , BMedSci, MBChB, PhD[12], Kim Edwards, MBBCh, DMRD[13], David J. Jenkinson, PhD[1], Nisha Sharma, MRCP[14], Elena Provenzano, MB BS, PhD[15], Bridget Hilton, BSc[3], Nigel Stallard , PhD[16], Alastair M. Thompson, BSc, MBChB, MD[17], Sian Taylor-Phillips , PhD[1,*], on behalf of the Sloane Project Steering Group

[1]Warwick Screening, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry CV4 7AL, United Kingdom
[2]Independent Cancer Patients' Voice, London, EC1R 0LL, United Kingdom
[3]Screening Quality Assurance Service, NHS England, Birmingham, B2 4BH, United Kingdom
[4]Cambridge Breast Unit and NIHR Cambridge Biomedical Research Centre, Cambridge University Hospitals NHS Trust, Cambridge CB2 0QQ, United Kingdom
[5]School of Cancer & Pharmaceutical Sciences, King's College London, Comprehensive Cancer Centre at Guy's Hospital, King's College London, London SE1 9RT, United Kingdom
[6]Breast Unit, Queen Elizabeth Hospital Birmingham and University of Birmingham, Edgbaston, Birmingham B15 2GW, United Kingdom
[7]Division of Cancer Sciences, School of Medical Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, M20 4BX, United Kingdom
[8]Oxford Breast Imaging Service, Churchill Hospital, Oxford OX3 7LE, United Kingdom
[9]Public Health Commissioning and Operations, Directorate of the Chief Operating Officer, NHS England, London, SE1 8UG, United Kingdom
[10]SW London Breast Screening Service, St George's University Hospitals NHS Foundation Trust, London, SW17 0QT, United Kingdom
[11]Association of Breast Surgery, Royal College of Surgeons of England, London WC2A 3PE, United Kingdom
[12]Department of Oncology and Metabolism, University of Sheffield, Sheffield S10 2RX, United Kingdom
[13]Breast Test Wales, Public Health Wales, Llandudno LL30 1QY, United Kingdom
[14]Breast Screening Unit, Seacroft Hospital, Leeds LS14 6UH, United Kingdom
[15]Histopathology and NIHR Cambridge Biomedical Research Centre, Cambridge University Hospitals NHS Foundation Trust, Cambridge CB2 0QQ, United Kingdom
[16]Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, Coventry CV4 7AL, United Kingdom
[17]Department of Surgical Oncology, Dan L Duncan Comprehensive Cancer Center, Baylor College of Medicine, Houston, TX 77005, United States

*Corresponding author: Sian Taylor-Phillips, PhD, Warwick Screening, Division of Health Sciences, Warwick Medical School, University of Warwick, Gibbet Hill Road, Coventry CV4 7AL, United Kingdom (s.taylor-phillips@warwick.ac.uk)

Abstract

Evidence-based clinical guidelines are essential to maximize patient benefit and to reduce clinical uncertainty and inconsistency in clinical practice. Gaps in the evidence base can be addressed by data acquired in routine practice. At present, there is no international consensus on management of women diagnosed with atypical lesions in breast screening programmes. Here, we describe how routine NHS breast screening data collected by the Sloane atypia project was used to inform a management pathway that maximizes early detection of cancer and minimizes over-investigation of lesions with uncertain malignant potential. A half-day consensus meeting with 11 clinical experts, 1 representative from Independent Cancer Patients' Voice, 6 representatives from NHS England (NHSE) including from Commissioning, and 2 researchers was held to facilitate discussions of findings from an analysis of the Sloane atypia project. Key considerations of the expert group in terms of the management of women with screen detected atypia were: (1) frequency and purpose of follow-up; (2) communication to patients; (3) generalizability of study results; and (4) workforce challenges. The group concurred that the new evidence does not support annual surveillance mammography for women with atypia, irrespective of type of lesion, or woman's age. Continued data collection is paramount to monitor and audit the change in recommendations.

Keywords: breast; mammography; early detection of cancer; health policy.

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Introduction

Epithelial atypia represents a group of diverse abnormalities of the breast including atypical ductal hyperplasia (ADH), flat epithelial atypia (FEA), atypical lobular hyperplasia (ALH), and lobular carcinoma *in situ* (LCIS), which are not malignant themselves but have been found to confer a 3 to 10 times increased risk of subsequent breast cancer over time.[1-3] Up to 35.7% of atypia identified on initial biopsy is upgraded to malignancy on excision[4] as cancer can coexist with the lesion.[5,6] Atypia is diagnosed in 5% to 10% of needle biopsies performed as part of the English NHS Breast Screening Programme (BSP)[5,7] and is increasingly managed with minimally invasive vacuum assisted excision (VAE) (ie, excise or sample thoroughly comparable to a diagnostic surgical excision[8]) and followed-up with annual mammographic surveillance for 5 years outside of the NHS BSP. This is followed by routine 3-yearly screening up to the age of 70 years with the option to self-refer for continued 3-yearly mammography thereafter. Annual surveillance imaging of these atypia cases provides a safety net to ensure no cancers are missed with VAE and is an opportunity for early cancer detection in higher-risk women.

Screen detected atypia is managed according to guidelines published by a multidisciplinary working group from an English Radiology, Surgery, and Pathology NHS Breast Screening Programme Co-ordinating Group in 2018.[8] The guidelines were based around existing evidence on upgrade rates to cancer on excision and long-term cancer risk. However, no evidence on the effectiveness of short-term regular surveillance mammography was available and the guidelines included a comment that this should be amended as "more data and national guidance become available."[8] Evidence-based clinical guidelines are informed by the best available evidence from research. They help to promote consistency, maximize patient benefit, reduce clinical uncertainty, and ensure resources are used appropriately. Evidence-based practice in the management of screen detected atypia should optimize early detection of cancer, address the increased risk of developing breast cancer and minimize the harm of over-investigation.

In response to this identified evidence gap, analysis of the data on screen-detected atypical hyperplasia of the breast collected as part of the Public Health England funded Sloane atypia project was started to better understand the clinical outcomes of atypia and use routine clinical data to inform evidence-based recommendations to help patients and healthcare professionals make more informed choices about management.[9]

Evidence from the Sloane atypia project prospective cohort

The Sloane atypia project is a prospective cohort of women with atypia diagnosed through the UK NHS BSP from April 2003 to the present.[9] Types of atypia included were ADH or atypical intraductal epithelial proliferation, FEA, and lobular *in situ* neoplasia (LISN), which includes ALH and LCIS. Data on this cohort were collected on radiology, histopathology, surgery, and radiotherapy proformas, to provide robust and generalizable evidence on the behaviour of atypia, and from which it would be possible to design tailored management strategies for individual patients with atypia. Data included age at diagnosis, mammographic features, biopsy method, histological features, surgical, and adjuvant treatment.

Subsequent development of breast cancer in this cohort was identified by matching women in the Sloane atypia project database to data held by the National Cancer Registration and Analysis Service (NCRAS) and information on mortality was added by linkage with the Mortality and Birth Information System.[10] This linkage was achieved using the NHS number and date of birth.

An observational analysis of the English Sloane atypia cohort up until 2018 was undertaken to explore how the number and type of breast cancers developed after detection of atypia.[13] This analysis was led by a team at the University of Warwick and supported by an expert group of clinicians, research managers of the Sloane project and patient representatives.

The analysis considered the following key questions:

1) How many women develop cancer after their diagnosis of atypia and when?
2) What type of cancers develop?
3) How many cancers are missed at atypia diagnosis?
4) Does the risk of developing cancer depend on the type of atypia?
5) How does this compare to screened women without an atypia diagnosis?

Full details of the analysis are reported elsewhere[13] but are briefly summarized here:

- The number of cancers post atypia diagnosis (at 3 and 6 years) were low and such cancers were similar to those in the general screening population, with similar ipsilateral and contralateral risk.
- Few cancers appeared to be missed at an atypia diagnosis and VAE did not result in more cancers missed than management with surgery.
- The number of cancers did not significantly differ by atypia type, breast density, or age after adjusting for year of diagnosis.
- Number of cancers at 3.5 years post atypia equated to the number of cancers in the general screening population.
- Cancer risk in more recent years was lower than the historical risk, probably due to the introduction of digital mammography which identifies more microcalcifications, a shift in atypia nomenclature and pathologists refining their diagnostic criteria, and an increase in size of the biopsy needle.

We confirmed from the analyses that, considering the short term, many atypia lesions may represent risk factors rather than true precursors of invasive cancer and concluded that annual mammography for 5 years after atypia diagnosis may not be beneficial for women in the current English NHS BSP. In addition, recent changes to mammography and biopsy techniques appear to identify cases of atypia which are more likely to represent overdiagnosis.

A wider expert group was convened to form a consensus based on these empirical results and to draft recommendations for consideration by policymakers on the management of women with screen detected atypia in the English BSP.

Methods

A half day consensus meeting was held in London in March 2023. This was organized and chaired by the research team

from the University of Warwick who undertook the analysis of the data.

The expert group totalled 20, and consisted of 3 radiologists, 1 radiographer, 2 breast pathologists, 4 breast surgeons, 1 clinical nurse specialist for breast screening, 1 patient representative from Independent Cancer Patients' Voice, the National Breast Screening Quality Assurance (SQAS) Lead, the Head of Public Health Commissioning and Operations, the National Breast Screening Programme Development Lead, the breast screening technical/systems product owner, intelligence and research lead, the National Breast Screening Programme Manager, 1 NHS England Breast Cancer Research Manager, and 2 researchers in evidence synthesis in breast screening.

Prior to the meeting, participants were sent a document summarizing the results of the Sloane atypia project observational analysis, alongside a prompt to submit key questions and concerns in relation to potential management changes of women with atypia that attendees would like to discuss. The research team used these prompts to develop example recommendations that reflect scenarios of doing more, the same, or less than current clinical practice (see Box 1) to facilitate discussion of the evidence. The example recommendations were developed with a focus on exploring the full range of options without any judgement of merit.At the consensus meeting, a summary of the Sloane atypia project and results from the analysis were presented, as well as a summary of voices from patient representatives collated from previous patient workshops (see Box 2). This was followed by discussions in small groups, using the example recommendations provided as prompts. This produced key features and preferences for recommendations, which were subsequently collated and discussed in the wider group. The Chair managed the discussion, identified areas of consensus and counted dissenting voices and noted their reasoning. Minutes were taken during these discussions. The aim of this paper is to present key considerations during the discussion of formulating recommendations, report the consensus recommendations from the expert group on the management of women with screen detected atypia, and note the number and reasoning of dissenting voices.

Results

Key considerations during the translation of study evidence into recommendations

Key considerations of the expert group in terms of the management of women with screen detected atypia were: (1) frequency and purpose of follow-up; (2) communication to patients; (3) generalizability of study results; and (4) workforce challenges.

1) Frequency and purpose of follow-up (annual mammography)

It was unanimously agreed that the evidence did not support more surveillance than is currently being provided within the first 5 years, namely annual surveillance for 5

Box 1. Example recommendations for the management of women with screen detected atypia. The example recommendations were based on key discussion points collated from attendees to consider, and included examples of doing more, the same, or less surveillance than current practice for women aged up to 70 years (routine screening age), women aged 71+, and any potential subgroups.

- No annual surveillance, only routine 3-yearly screening until age 70, standard opportunity for self-referral for 71+.
- No annual surveillance, only routine 3-yearly screening until age 70, standard opportunity for self-referral for 71+ except for women aged 68+ at time of atypia diagnosis who will continue with routine 3-year screening for 3 additional rounds.
- No annual surveillance, only routine 3-yearly screening until age 70 with information on atypia risk and message to imply importance of attending future screening invitations, standard opportunity for self-referral for 71+.
- Annual surveillance for 5 years then routine 3-yearly screening until age 70, standard opportunity for self-referral for 71+.
- No annual surveillance only routine 3-yearly screening but extended post 70 years.
- Two yearly routine screening until age 70, standard opportunity for self-referral for 71+.
- Two yearly screening for rest of life.
- One screen at 1 year post atypia for reassurance for women then routine 3-yearly screening until age 70, standard opportunity for self-referral for 71+.
- Routine 3-yearly screening until 6 years post atypia then annual surveillance for 5 years followed by routine 3-yearly screening up to 70 years, standard opportunity for self-referral for 71+.
- Annual surveillance for 3 years than routine 3-yearly screening until age 70, standard opportunity for self-referral for 71+.
- Annual surveillance for 5 years followed by 2-yearly screening for rest of life.
- No annual surveillance, only routine 3-yearly screening until age 70 with endocrine therapy.
- Annual surveillance for 5 years then routine 3-yearly screening until age 70 with endocrine therapy, standard opportunity for self-referral for 71+.
- No annual surveillance, only routine 3-yearly screening until age 70 with prophylactic anti oestrogens for women with very dense breasts, standard opportunity for self-referral for 71+.
- Annual surveillance for 5 years then routine 3-yearly screening until age 70 with prophylactic anti oestrogens for women with very dense breasts, standard opportunity for self-referral for 71+.
- Annual surveillance for 5 years then routine 3-yearly screening until age 70 for mixed atypia routine 3-yearly screening for all other atypia types until age 70, standard opportunity for self-referral for 71+.
- No annual surveillance only routine 3-yearly screening but extended post 70 years for women with mixed atypia.

Box 2. Patient voices ($n = 5$) were collected during 2 workshops in July 2022, to understand how women may perceive and understand potential new recommendations. These were attended by 5 patient representatives and run collaboratively with the project's patient and public involvement advisor and the research team at the University of Warwick.

Women agreed that breast screening was essential and that timings should be based on evidence.

Current management

- Women interpret the screening age of a screening programme as their time at risk.
- Cancer patients feel that when yearly surveillance stops, their care stops: "*Screening every year for 5 years, then that's it, there is just nothing for you.*"
- Women thought it "*unfair*" that practice varied for atypia follow-up in different parts of the country.

Communication and information

- Communication from clinicians not sufficient: "*If screening can pick something up it ought to be in the book.*"
- Women feel that "*Clinicians should not know more about me than I do.*"
- Information on atypia should be provided, either when recalled or when atypia is diagnosed, with a separate leaflet: "*If you are going to tell women they have atypia you can't abandon them, you need to follow them.*"

Future management

- Screen 1 year after atypia for reassurance that "*nothing has changed*" when worry is greatest.
- Considering the study findings, 5 years of annual screening "*seems a bit mad.*"
- Some preferred to have option to have annual screening later on, or regular screening after 5 years and post 70 years of age.

years then routine 3-yearly screening until age 70, with standard opportunity for self-referral for 71+. Furthermore, it was agreed that the new pathway should be as simple as possible.

Just over half (11/20, 55%) of the participants thought that there was no evidence to support screening over and above current routine 3-yearly screens for women under the age of 71 years. Less than half (8/20, 40%) of attendees supported a single additional screening invitation at 1 year post atypia diagnosis "for reassurance" and one attendee (1/20, 5%) supported a 2-yearly screening programme for all women with atypia.

While screening for reassurance at 1 year was mentioned as a response to patient views, the group quickly agreed that better communication with patients would be preferred over screening for reassurance. This was due to:

1) the experience that additional investigations, such as surveillance mammography, would not necessarily find more cancers,
2) the concern over conveying mixed messages, as discussed further below (the need of reassurance stems from the worrying message of being at increased risk),
3) other radiographic findings that may convey a potential increased risk, such as extremely dense breasts, do not prompt intense mammographic follow-up within the NHS BSP, and
4) there is no data on psychological harm from surveillance to counter any potential benefit.

Screening to reassure clinicians was discussed, that is, to alleviate the worry of missing/not sampling a pre-existing cancer, despite the new evidence. This was the primary driver in those who advocated screening at 1 year. It was hypothesized that current guidance for surveillance mammography was a response to uncertainty as to whether women with atypia are at increased risk of having a cancer diagnosed in the short term and whether the move from surgery to VAE would miss cancers. The new data provides much more evidence that the short-term risk of missing or developing cancer is low.[13] In order to provide the reassurance that clinicians need, the group decided that data on interval cancers should be investigated to determine the proportion of interval cancers that had a previous B3 diagnosis (lesion with uncertain malignant potential, which includes those with an atypia). A small number of interval cancers would confirm that the Sloane atypia data is representative of the general screening population without additional missed cancers. On the basis of this discussion, there was agreement that screening for reassurance of clinicians was not a favoured option.

There was consensus that women who would have no further routine screening invitations (those aged 68 to 70 at the time of their atypia diagnosis) should not be managed differently to women at a younger age where further screening invitations would be routine. It was discussed that in Wales, women with atypia are offered screening every 2 years up to the age of 70 and then self-refer after the age of 70.[11] The 2-yearly screening offer (in line with standard population screening in Europe), is well-received. The decision on 2-yearly screening was based on evidence from the United States on long-term risk from women diagnosed many years ago, and the risk may not apply to more recent diagnoses. It was noted that the Sloane atypia project analysis does not provide evidence around 2-yearly screening and insufficient data on longer-term risk. The group agreed that this represents a research priority for the future.

2) Communication

Patients believed that better communication of diagnoses and risk will improve knowledge and empower women to make more informed decisions. Lack of knowledge and ambiguous management of women with atypia is a cause for confusion amongst patients. This is because patients are told that they have not got cancer but may develop cancer in the future, without information on timing. The need for more intense follow-up can be unsettling, cause long-term anxiety[12] and may not necessarily reassure. Without a rationale to stop surveillance after 5 years, this short-term intense management is incomprehensible. This has a negative psychological impact

on patients.[12] The group viewed this new evidence as an opportunity to improve patient communication and be consistent in the clinicians' message to patients, so that their actions would match their words. There was discussion around whether patients should be told about atypia at all. It was felt that since atypia has been acknowledged as an entity for a long time and will require VAE as an intervention, discussion about these lesions and the need for further investigation to exclude cancer is valid, prior to intervention. There should then be an unambiguous message post excision.

The group felt strongly that communication should include information on the option to self-refer for screening post 70 years which may be particularly important in this group of women.

In addition to improving communication to individual women the group also agreed that the general communication about the change in recommendations needs to be carefully developed to avoid potential interpretation that service provision is being removed. The change in guidance needs to be communicated as a positive outcome in response to improved knowledge. Finally, this communication needs to extend to clinicians to ensure their acceptance.

3) Generalizability of study results

There was concern that, even though overall 63/77 (81.8%) English breast screening centres contributed data to the Sloane atypia project, this fluctuated over the study period and these findings may, therefore, not be applicable across all of England. The group raised the question as to whether higher performing centres were more likely to submit atypia data to the Sloane atypia project and whether data may be biased and results not generalizable. If this was the case, the results could not be used for policy change. It was noted that for periods with more complete data, there were lower rates of subsequent cancer in the years following an atypia diagnosis. A similar pattern, of historical higher, but more recent lower cancer rates after an atypia diagnosis, was seen when considering all centres and when restricting analyses to those centres that submitted all atypia cases throughout.[13] Therefore, more complete data submission from higher performing screening centres is unlikely to have biased the data. However, there was strong agreement that, whichever approach would be taken forward into clinical guidance and practice, there was a need to continue data collection for audit and further research.

The second aspect around generalizability was the consideration of differences in breast screening programmes across the world. The group felt it was important to highlight that the recommendations made are based on the English system, with a tightly quality assured screening programme, routine assessment of clinical skills, comprehensive guidelines, universal use of digital mammography, and VAE of indeterminate lesions.

4) Workforce considerations

The group briefly considered that, if fewer mammograms were performed than is current practice, it would help with demand-capacity balance in breast screening and would ensure resources are used efficiently to assess and manage lesions in a timely fashion and that the system is currently under enormous pressure. However, the group agreed that the focus needs to be on what is best for the patients and not what is most practical and feasible.

Recommendations

The group decided with a majority of 17/19 (89.5%, one person had left), that the present evidence suggested that annual surveillance mammography for the first 5 years is not beneficial for women with atypia, irrespective of the atypia type, or women's age. This was with the caveat that the data on interval cancers supported this. They recommended that women with screen detected atypia should be offered routine 3-yearly screening with a clear message that thorough investigation has shown that they do not have cancer and therefore management should be the same as for those without cancer.

Women due to have no further routine screening invitations (those aged 68 to 70 at the time of their atypia diagnosis) should receive the same assessment and care as those in the younger age group but should also be given information on the option to self-refer for breast screening similar to the general screening population of that age without atypia.

Two participants at this point were not in agreement. One participant voiced their concern over the long-term risk associated with all B3 diagnoses. The second dissenting participant interpreted the 3-year risk as sufficiently high to justify more intensive follow-up. Both participants would like to see 2-yearly screening for women with atypia. However, no evidence for such a strategy is currently available.

The group agreed that the new recommendations should take a phased approach and that women who are currently undergoing 5-year annual surveillance should continue surveillance.

The group agreed on the following requirements alongside the recommendations

1) Ongoing data collection from all screening centres with the new pathway implemented, to monitor the guideline in practice and to ensure continued research to support the recommendation.
2) The pathway should be the same across England for all screening centres.
3) Communication of the evidence around cancer risk that informed the guideline to clinicians including primary care, patients, and the wider public needs to be improved significantly.

The group highlighted the following caveats of the recommendations

1) These recommendations are based on the assumption that national guidance is being followed and that women with screen-detected atypia who (as a result of this evidence) will be told that their risk is the same as the general screening population have had a vacuum assisted (or less commonly surgical) excision.
2) The study focused on short-term risk to fill the evidence gap around 5-year surveillance mammography. Therefore, an update on long-term risk cannot be concluded from this study and the group agreed that there is a long-term risk for women with atypia as evidenced in the literature. This should be a research priority for the future.

3) The group also noted that there were no data in this analysis of patients diagnosed with LCIS which, due to the small numbers, were grouped within the broader group of LISN (the range from ALH and LCIS). Therefore, management should not be different for women with LCIS than for other patients with atypia.

The group agreed on the following future research priorities

1) The long-term cancer risk for women with screen detected atypia.
2) Two-yearly screening as an alternative for women with screen detected atypia.

Conclusion

Based on the evidence presented, the majority (17/19, 89.5%) of the expert group felt that women with atypia should not have annual surveillance for the first 5 years and instead revert to routine surveillance every 36 months within the breast screening programme. The importance of clear communication and continued data collection was also felt to be of vital importance. Caveats around these recommendations require ongoing data collection for audit and research. Generalization of these recommendations to breast screening programmes outside the UK NHS BSP would require assessment of similarities and differences in their quality assurance, imaging modalities, and excision guidelines. Looking beyond the immediate implications of this project, we demonstrate that routine data collection to inform policy and improve the NHS BSP is both feasible and worthwhile.

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Conflicts of interests

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Data availability

Data are held by NHS England. Access to the Sloane project data from external parties is governed by application to the Breast Screening Research Innovation and Development Advisory Committee (RIDAC). Data will only be released by the Sloane Project to researchers under approval and in an anonymized or depersonalized format and under a data sharing agreement.

Ethics approval

The Sloane Atypia observational analysis received research ethics approval from the University of Warwick Biomedical and Scientific Research Ethics Committee (BSREC 10/20-21, 8 October 2020), Public Health England office for data release approvals (ODR1718_313) and approval from the English Breast Research Advisory Committee (BSPRAC_031). Informed consent from individual participants was not required.

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