Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Protocol for a Health Technology Assessment of modifications to the BreastCheck programme

Workstream 1 (of 2): Consideration of screening pathways that incorporate breast density

12 March 2026

About the Health Information and Quality Authority

The Health Information and Quality Authority (HIQA) is an independent statutory body established to promote safety and quality in the provision of health and social care services for the benefit of the health and welfare of the public.

Reporting to the Minister for Health and engaging with relevant government Ministers and departments, HIQA has responsibility for the following:

- **Setting standards for health and social care services** — Developing person-centred standards and guidance, based on evidence and international best practice, for health and social care services in Ireland.
- **Regulating social care services** — The Chief Inspector of Social Services within HIQA is responsible for registering and inspecting residential services for older people and people with a disability, and children's special care units.
- **Regulating health services** — Regulating medical exposure to ionising radiation**.**
- **Monitoring services** — Monitoring the safety and quality of permanent international protection accommodation service centres, health services and children's social services against the national standards. Where necessary, HIQA investigates serious concerns about the health and welfare of people who use health services and children's social services.
- **Health technology assessment** — Evaluating the clinical and cost effectiveness of health programmes, policies, medicines, medical equipment, diagnostic and surgical techniques, health promotion and protection activities, and providing advice to enable the best use of resources and the best outcomes for people who use our health service.
- **Health information** — Advising on the efficient and secure collection and sharing of health information, setting standards, evaluating information resources and publishing information on the delivery and performance of Ireland's health and social care services.
- **National Care Experience Programme** — Carrying out national service-user experience surveys across a range of health and social care services, with the Department of Health and the HSE.

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List of abbreviations used in this report

ABUS	automated breast ultrasound
ACR	American College of Radiology
AMSTAR	A MeaSurement Tool to Assess Systematic Reviews
BI-RADS	Breast Imaging-Reporting and Data System
BMI	body mass index
CEM	contrast enhanced mammography
CSO	Central Statistics Office
DBT	digital breast tomosynthesis
DCIS	ductal carcinoma in-situ
EAG	expert advisory group
ECIBC	European Commission Initiative on Breast Cancer
EEA	European Economic Area
EU	European Union
EUnetHTA	European Network for Health Technology Assessment
GRADE	grading of recommendations, assessment, development and evaluation
HSE	Health Service Executive
HIQA	Health Information and Quality Authority
HTA	health technology assessment
INAHTA	International Network of Agencies for Health Technology Assessment
MRI	magnetic resonance imaging
NSAC	National Screening Advisory Committee
PICOS	Population, Intervention, Comparison, Outcome, Study design (Framework for identifying the scope of a review question)

1. Introduction

1.1 Background

The National Screening Advisory Committee (NSAC) was established in 2019 by the Minister for Health as an independent advisory committee to play a significant strategic role in developing and considering population-based screening programmes in Ireland. Since 2020, at the request of the Department of Health, the Health Technology Assessment (HTA) Directorate within the Health Information and Quality Authority (HIQA) has undertaken evidence synthesis and provided evidence-based advice to NSAC on behalf of the Minister for Health.

1.2 Condition and screening programme

Breast cancer was the most commonly diagnosed invasive cancer and the second leading cause of cancer mortality among females in Ireland during 2020–2022.[1] As life expectancy continues to increase and as the population continues to expand in Ireland, it is projected that breast cancer incidence will increase by approximately 50% by 2045, compared to 2015.[2] The strongest risk factors for breast cancer are female sex and increasing age. Other risk factors include hormonal and reproductive factors, breast density, hereditary and genetic factors, alcohol consumption, body mass index (BMI), and environmental exposures.[3, 4] It is estimated that approximately 5–10% of breast cancer cases are attributable to hereditary and genetic risk factors.[5] A US-based study found that 45% of breast cancer cases among women aged 40 to 74 years in the Breast Cancer Surveillance Consortium can be explained by known risk factors.[6] These include family history of breast cancer, body mass index, history of benign breast disease, age at first birth, and breast density.[6]

Breast cancer screening aims to reduce breast cancer morbidity and mortality among asymptomatic women through the earlier detection and treatment of ductal carcinoma in-situ (DCIS) and invasive breast cancer.[7] The Council of the European Union has recommended breast screening for women aged 50 to 69 years since 2003.[8] In 2022, a lower age limit of 45 years and upper age limit of 74 years were suggested by the Council of the European Union,[9] based on recommendations from the European Commission Initiative on Breast Cancer (ECIBC).[10] The Council of the European Union notes, however, that decisions regarding screening at the Member State level additionally take into consideration factors such as disease burden, healthcare resources available, the benefit-harm balance and cost-effectiveness of cancer screening, and experience from scientific trials and pilot projects.[9] In Ireland, BreastCheck, the national population-based breast screening programme, invites

eligible asymptomatic women aged 50 to 69 years for a mammogram every two years.

1.2.1 Breast density

Breast density refers to the amount of fibroglandular (dense) tissue relative to the amount of adipose (fatty) tissue in the breast.[11] Women with dense breasts have an increased risk of developing breast cancer compared to women with non-dense breasts.[12, 13] Breast density changes over time, and, typically, younger women have denser breast tissue.[14] The greatest decline in breast density can be observed over the menopausal transition.[14] Breast density can be influenced by age, BMI, genetic factors, ethnicity, age at menarche (when menstrual periods begin), reproductive factors, use of hormone replacement therapy, and alcohol consumption.[15-20]

On a mammogram (an x-ray of the breast), dense tissue appears white, similar to breast cancer tumours, while adipose tissue is radiolucent (x-rays pass through adipose tissue with minimal attenuation) and appears dark.[11] As a result, high levels of dense tissue can mask the appearance of breast cancer tumours on a mammogram, which reduces the sensitivity of mammography for women with dense breasts.[21]

Breast density can be measured using visual, semi-automated, and automated methods.[22, 23] Visual methods involve a radiologist visually assessing breast tissue composition on a mammogram. The Breast Imaging-Reporting and Data System (BI-RADS®) breast composition classification system developed by the American College of Radiology (ACR) is the most widely used in clinical settings to describe the amount of dense tissue in the breast visible on a mammogram.[24] Due to the subjective nature of visual breast density measurement methods, they are limited by substantial inter- and intra-reader variability.[23, 25] Semi-automated and automated breast density measurement tools aim to overcome these reproducibility limitations.[22] However, there is a lack of consensus regarding which breast density measurement tool is the most reliable and reproducible, and can be easily implemented in a clinical setting.[26, 27]

Internationally, there has been increased interest regarding the introduction of screening pathways for women with dense breasts. These may include measuring, recording and notifying women of their breast density, and offering alternative screening pathways. For women with dense breasts and a negative screening mammogram, these pathways may involve offering more frequent screening with digital mammography, an alternative to digital mammography as the primary screening modality in subsequent screening rounds (substitution), or an additional screening exam with an alternative imaging modality following the primary screening

mammogram (supplemental screening). Potential alternative imaging modalities may include digital breast tomosynthesis (DBT), ultrasound, magnetic resonance imaging (MRI), or contrast-enhanced mammography (CEM).

In 2023, the European Commission Initiative on Breast Cancer (ECIBC) published guidance on adapted screening strategies for asymptomatic women with high breast density.[10] Two conditional recommendations were issued in favour of the use of DBT as the primary screening modality for women with dense breasts (substitution), and implementing tailored screening with additional DBT for those with high breast density (supplemental screening).[10] These recommendations were based on 'low' and 'very low' quality evidence, respectively, due to uncertainty in the estimates for false positives, invasive breast cancers and interval breast cancers, and a lack of evidence demonstrating the impact on breast cancer mortality. Conditional recommendations were issued against supplemental screening with MRI or ultrasound based on very low certainty evidence.[10] Recent reviews highlight international variation in screening practices for women with dense breasts, and an absence of consensus among international breast cancer screening guidelines that incorporate breast density.[28, 29] Breast density is not currently measured or reported as part of the standard BreastCheck screening pathway in Ireland.[30]

1.3 HTA of modifications to the BreastCheck programme

In response to submissions received as part of the NSAC calls for submissions, NSAC requested that HIQA examine the evidence for extending the age of eligibility for the BreastCheck programme to those aged 45 to 49 and 70 to 74 years, in line with the European Commission Initiative on Breast Cancer (ECIBC) guidelines. The request further outlined the need for consideration of breast density. The assessment was prioritised by NSAC in 2023, for commencement following the HTA of extending BowelScreen to those aged 50 to 54 years.

As breast density notification and age extension are distinct questions, these will be considered in two separate, though related, workstreams. Workstream 1 will consider screening pathways that incorporate breast density. Workstream 2 will assess the clinical and cost effectiveness of extending BreastCheck to those aged 45 to 49 and 70 to 74 years, as well as assessing the budget impact, organisational implications and ethical issues associated with an age extension to the programme.

1.3.1 Workstream 1 (of 2): Consideration of screening pathways that incorporate breast density

The scope of the assessment for this workstream was agreed with NSAC, and is limited to considering:

- screening pathways that incorporate breast density measurement and notification for all BreastCheck participants
- screening pathways that incorporate supplemental screening for women with dense breasts, in addition to breast density measurement and notification for all BreastCheck participants.

The present protocol relates to Workstream 1. A separate protocol will outline the approach to the assessment of Workstream 2 (extending the BreastCheck programme to women aged 45 to 49 years and 70 to 74 years).

2. Evidence synthesis approach

HTA is a multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle. The purpose is to inform decision-making in order to promote an equitable, efficient, and high-quality health system.[31]

HIQA HTAs typically include the following domains:

- epidemiology
- description of the technology
- clinical effectiveness and safety
- costs and economic evaluation
- organisational considerations
- social and ethical implications.

The mapping of these domains to the NSAC *Criteria for Appraising the Viability, Effectiveness and Appropriateness of a Screening Programme* is outlined in the Appendix (Table A.1).

A phased approach will be adopted for this assessment. The first phase will focus on synthesising the available evidence for the following domains: epidemiology, description of technology, clinical effectiveness and safety, and social and ethical implications. Subject to the findings from phase one and following deliberations by NSAC, a second phase may be undertaken to assess the economic and organisational implications of incorporating breast density within the BreastCheck pathway.

This protocol focuses on the first phase of Workstream 1.

2.1 Aims and objectives

The aim of phase one of this assessment is, broadly, to consider the benefits, harms, and ethical implications of considering screening pathways that incorporate breast density within the BreastCheck programme.

The objectives are as follows:

- describe the epidemiology of breast density, including breast cancer risk and outcomes
- describe approaches to the measurement and classification of breast density
- describe the test accuracy of digital mammography for the detection of breast cancer according to breast density
- conduct a review of international policy and guidelines on breast density notification and supplemental breast cancer screening based on breast density
- describe the following screening pathways for women in Ireland as part of the BreastCheck programme:
    - the current screening pathway
    - potential pathways that incorporate breast density notification and also include supplemental screening for women with dense breasts
    - potential pathways that incorporate breast density notification only
- review the clinical effectiveness and safety of breast density notification and supplemental screening for women with dense breasts, including consideration of the accuracy of supplemental screening
- consider any ethical or societal implications that breast density notification or supplemental screening for women with dense breasts may have for individuals, families, the general public or the healthcare system in Ireland.

2.2 Establishment of the Expert Advisory Group

In line with HIQA guidelines for stakeholder engagement, an appropriately represented multidisciplinary expert advisory group (EAG) will be convened to ensure that the assessment takes into account all relevant and important issues from the perspectives of multiple stakeholders.[32] The EAG provides a key source of expertise to advise the Evaluation Team and inform the interpretation of the evidence and development of the advice to NSAC. The EAG will comprise nominees from a range of stakeholder organisations, including patient and public representation, healthcare providers, managers and policy makers, and clinical and methodological experts. The

role of the group is to inform and guide the process, provide expert advice and information, and to provide access to data where appropriate.

3. Description of technology

The purpose of this chapter is to provide an overview of breast cancer screening for women with dense breasts.

3.1 Breast cancer screening

A description of breast cancer screening and the existing screening pathway in the BreastCheck programme in Ireland will be provided. This section will consider the test accuracy of digital mammography, the primary screening modality for the BreastCheck programme in Ireland, and how it varies according to breast density. To inform this section, a review of national and international literature, including statistical reports from the BreastCheck programme, will be conducted.

3.2 Breast cancer screening for women with dense breasts

3.2.1 Potential screening pathways that incorporate breast density

This section will outline potential approaches to the measurement and classification of breast density, and potential options for notifying screening participants about their breast density. The possible forms the notification may take, such as a letter or phone call, the type of information that may be included, and the possible next steps after receiving this information, will be considered. A description of the potential imaging modalities (DBT, ultrasound, MRI with contrast, and CEM) for screening women with dense breasts will also be provided.

3.2.2 Review of international guidelines and practice

This section will provide an overview of current international breast cancer screening guidelines and practice related to breast density notification and modified breast screening pathways based on breast density. Grey literature sources (for example, national public health organisations and the websites of governmental departments and relevant agencies) and recent peer-reviewed literature will be reviewed using scoping methodology.

The specific objectives of this review will be to:

1. identify breast cancer screening guidelines from professional societies or organisations that incorporate breast density

2. describe countries that currently have a breast cancer screening programme and screening pathways incorporating breast density in place.

International breast cancer screening guidelines that specify or include breast density will be examined. Guidelines intended for use or considered transferable to the European context, or that inform the development of other international guidelines, such as those developed by the United States Preventive Services Task Force, will be considered eligible for inclusion. Where possible, specific recommendations related to breast cancer screening and breast density will be extracted. This will include recommendations that refer to breast density measurement methods and classification systems, breast density notification, and alternative imaging modalities for women with dense breasts.

The review of international practice will focus on European countries considered most relevant to Ireland, and high-income countries as classified by the World Bank, with organised breast cancer screening programmes. Specific information relating to existing screening programmes and screening pathways incorporating breast density will be extracted. This will include, but is not limited to: the classification system and measurement method for breast density; if participants receive a breast density notification; and information in relation to supplemental breast screening for women with dense breasts. Other noteworthy elements of each relevant programme will also be extracted.

4. Epidemiology

The purpose of this chapter within the assessment is to provide a brief summary of the epidemiology of breast cancer, and a detailed overview of the epidemiology of breast density. The specific aims of this chapter will be to describe:

- the natural history and epidemiology of breast cancer
- the aetiology and distribution of breast density
- the prevalence of dense breasts among women as defined by the ACR BI-RADS® breast density classification system[24]
- the incidence and prevalence of breast cancer according to breast density
- breast cancer characteristics and outcomes (that is, morbidity and mortality) according to breast density.

Where available, national datasets will be used to estimate breast cancer outcomes in Ireland. Data from annual reports and publications by the National Cancer Registry Ireland will be used to describe breast cancer incidence, mortality and survival.

Population data from the Central Statistics Office (CSO) will be used to estimate the number of people eligible for BreastCheck. Based on initial scoping, it is not expected that local data will be available to estimate the distribution of breast density and prevalence of dense breasts among women in Ireland. However, the number of individuals with dense breasts eligible for screening in BreastCheck in Ireland will be estimated by applying international estimates from randomised controlled trials and population-based observational studies to Irish population data. Data from the international literature will also be presented to understand the risk of developing breast cancer according to breast density, and the impact of breast density on breast cancer patient characteristics (such as mode of detection, cancer stage, treatment) and outcomes (such as survival).

5. Clinical effectiveness and safety

5.1 Clinical effectiveness and safety of breast density notification without formal provision of supplemental screening

The primary impact of breast density notification on health outcomes is mediated through receipt of additional or alternative imaging to counter the reduced sensitivity of digital mammography for detecting breast cancer in women with dense breast tissue. Early identification makes cancers easier to treat, increasing survival.[33] The potential benefits of additional or alternative imaging must be counterbalanced against the potential harms, which may include an increase in malignancy arising from increased radiation exposure, reactions to contrast media used in the imaging process, adverse effects from overtreatment of benign lesions or cancers that would have never have manifested clinically, and psychological harm and anxiety arising from false positive findings.[34]

With or without additional or alternative imaging, it is possible that breast density notification could also have an effect on health in its own right. In theory, positive effects might include allowing participants to be more 'breast aware', leading to changes in healthcare utilisation and improved outcomes. However, notification may also have negative effects. For example, some studies have linked notification to psychological harms.[35] This chapter will narratively review the evidence on the effectiveness and safety of breast density notification, focusing on breast cancer

morbidity and mortality, breast cancer detection rates, interval cancer rates, stage at diagnosis, and anxiety. However, scoping indicated that there is limited evidence on these outcomes. Further, there is potential for notification to introduce inequity if supplemental screening can only be accessed privately by those who can afford to pay. For these reasons, the impact of breast density notification on other outcomes, such as knowledge and awareness of breast density, supplemental screening or mammography re-screening rates, will be considered in more detail in the chapter on ethical, patient and social considerations (section 6).

The approach taken to assess the effectiveness and safety of supplemental screening for those with dense breasts is described in section 5.2, while methods for a review of substitution from digital mammography to an alternative screening modality are described in section 5.3.

5.2 Clinical effectiveness and safety of supplemental screening

5.2.1 Preliminary scoping and review questions

Preliminary scoping identified a recent HTA published by Ontario Health, which included a comprehensive review of the clinical effectiveness of supplemental screening.[34]

The Ontario Health review set out to answer the following research questions:[34]

1. What are the sensitivity and specificity of supplemental breast screening with ultrasound, DBT, MRI or CEM, as an adjunct to mammography for breast cancer screening in people with dense breasts?

2. What are the comparative sensitivity and specificity of supplemental breast screening with ultrasound, DBT, MRI, or CEM, as an adjunct to mammography, compared to mammography alone for breast cancer screening in people with dense breasts?

3. What are the effectiveness and harms of supplemental breast screening with ultrasound, DBT, MRI, or CEM as an adjunct to mammography compared to mammography alone for breast cancer screening in people with dense breasts?

While the review was not defined by the study authors as a systematic review, it followed many systematic review methods. The review was formally quality appraised using A MeaSurement Tool to Assess Systematic Reviews (AMSTAR) Version 2.[36] While a number of limitations were identified, the review addressed key criteria, including a comprehensive search strategy, assessment of the risk of bias, and considered the impact of both risk of bias and heterogeneity when describing results.

Given its alignment with the present review, the methodological rigour and the recency of its search (October 2021), a decision was made to update the Ontario Health Review for this HTA.

5.2.2 PICOS framework

The inclusion and exclusion criteria for this review are outlined in Table 1. This HTA closely replicates the review question of the Ontario Health Review in terms of the *Population, Intervention, Comparator, Outcome, Study design* (PICOS) framework.

With regards to the intervention, the present review is narrower in that MRI without contrast is excluded as an intervention, given there is very little evidence of its use for breast imaging in any setting (diagnostic and screening). Also, Ontario Health conducted an analysis of the effectiveness and safety of ultrasound by collating the evidence for both automated breast ultrasound and handheld ultrasound together, as well as analysing them separately. However, for the purposes of this review, they will be considered as distinct screening modalities only.

The present review is broader than the Ontario Health review in that additional outcomes have been added including "overdiagnosis" and "any adverse event". Two outcomes ("characteristics of interval cancers detected" and "biopsy rate"), that were not pre-specified by the Ontario Health review but were collected by them, are prespecified for the current update.

Table 1. Inclusion and exclusion criteria for assessing the clinical effectiveness of supplemental screening

	Inclusion criteria	Exclusion criteria
Population	▪ Asymptomatic people aged 40 years or older ▪ Negative or benign breast screening mammography results (BI-RADS assessment category 1 or 2) ▪ No high-risk factors ▪ Dense breasts (defined as > 50% or ≥ 75% dense tissue, BI-RADS composition categories **C** and or **D** or equivalent, regardless of method of density determination[†] [for example visual, quantitative, or automated software/artificial intelligence]).	▪ Participants with high-risk factors (for example known high-risk genetic mutations; a family history of high-risk genetic mutations or cancer; a ≥ 25% lifetime risk of breast cancer;[‡] or a history of chest radiotherapy) ▪ Participants defined as high-risk by the study authors ▪ Participants with male breast cancer ▪ Participants younger than 40 years ▪ Population in which breast density was not reported, or that included those with and without high breast density and the characteristics of the target population (and their results) could not be extracted.
Intervention	Supplemental screening after 2-dimensional digital or film mammography with one of: ▪ Contrast-enhanced (spectral) mammography ▪ Handheld ultrasound ▪ ABUS ▪ DBT (also known as 3-D mammography) ▪ MRI: with contrast, full MRI or abbreviated MRI.	Imaging for: ▪ Surveillance (for example recurrence or progression) ▪ Diagnosis ▪ Staging ▪ Prognosis ▪ Risk stratification ▪ Other purposes not related to screening.
Comparator	For sensitivity and specificity ▪ comparator test (screening mammography alone) ▪ clinical reference standard (histopathological confirmation of cancer). For recall rate, cancer detection rate: ▪ screening mammography alone ▪ comparisons between eligible supplemental imaging modalities ▪ clinical reference standard (histopathological confirmation of cancer).	Imaging modalities for primary screening (for example, compared to mammography as a replacement).

	Inclusion criteria	Exclusion criteria
	For all other effectiveness outcomes: ▪ screening mammography alone ▪ comparisons between eligible supplemental imaging modalities.	
Outcome	▪ Sensitivity ▪ Specificity ▪ Interval cancer rate ▪ Incremental cancer detection rate of supplemental screening ▪ Prognostic features of cancers detected by supplemental screening (for example invasive, DCIS, nodal status, tumour size, stage) ▪ Prognostic features of interval cancers ▪ Abnormal recall rate ▪ Biopsy rate ▪ Adverse effects (all) o Adverse reactions to contrast media o Psychological impact, distress, anxiety ▪ Overall or breast cancer-specific mortality or survival. ▪ Overdiagnosis ▪ Health related quality of life.	
Study design	▪ Studies published since 1 January 2015 ▪ English language full-text publications ▪ Systematic reviews (including meta-analyses and health technology assessments that included a systematic review) of comparative studies (randomised controlled trials and nonrandomised studies) that matched our research question and population, intervention, comparator, and outcomes. Systematic reviews with a broader scope will be considered to be eligible, provided that they included relevant results.§ ▪ Primary studies: prospective comparative studies (randomised controlled trials and nonrandomised studies); if none,	▪ Noncomparative case-control/two-gate diagnostic studies ▪ Modelling, reader, or simulation studies ▪ Technical validation, laboratory, animal, or in vitro studies ▪ Narrative or nonsystematic reviews, editorials, commentaries, case reports, conferences abstracts and posters, letters.

	Inclusion criteria	Exclusion criteria
	retrospective nonrandomised comparative studies: ○ Comparative test accuracy studies (primary cohort or cross-sectional studies; paired or randomised designs) in which all study participants received both mammography and the index test (i.e., supplemental imaging modality), followed by verification of disease by the reference standard ○ Single-test accuracy studies (for example, primary cohort or cross-sectional studies where the reference standard was histological confirmation of cancer) with either false-positive/ false-negative rates or sufficient information to construct a 2 × 2 table (true positives, true negatives, false-positives, false-negatives) to calculate sensitivity and specificity.	

† Breast density can be determined using visual, quantitative, or automated software/artificial intelligence.

‡ Risk prediction may be based on IBIS (International Breast Cancer Intervention Study breast cancer risk prediction tool), BOADICEA (Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm) or a similar tool.

§ Systematic reviews had to have clearly reported literature search methods, including (at a minimum) information about the databases searched, search terms, and search dates; they also had to provide explicit prespecified eligibility criteria.

Key: ABUS, automated breast ultrasound, BI-RADS – Breast imaging reporting and Data System, DBT – digital breast tomosynthesis, DCIS – ductal carcinoma in situ, MRI – magnetic resonance imaging.

Subgroup analysis

The Ontario Health Review predefined a number of subgroup analyses.[34] However, because of a lack of available data, the authors were only able to conduct a prespecified subgroup analysis for the comparison of automated breast ultrasound (ABUS) with handheld ultrasound using data from one study. For the purposes of this review, handheld ultrasound and ABUS will be analysed as separate modalities in the first instance. Therefore, a subgroup analysis will not be required. The following subgroups are predefined for the current review:

- heterogeneously dense (BI-RADS® category **C** or 51%–75% density) versus extremely dense (BI-RADS® category **D** or >75% density)
- people with a personal history of breast cancer
- age
- frequency of screening.

5.2.3 Identification of studies

The Ontario Review search strategy was reviewed by a librarian and replicated on 16 October 2025 in Medline and Embase via Ovid, and the Cochrane Library CENTRAL database to identify studies published since the last search of the Ontario review (29 October 2021). The complete electronic search strategy for all databases is available on Zenodo.[37] For new outcomes, the search for relevant evidence published prior to October 2021 is limited to studies identified in the Ontario Health review.

Reference lists of included studies will be searched for potentially relevant citations. Forward citation searching of the clinical review and of included studies will be performed using the Citationchaser package (via the associated Shiny app). The grey literature search will examine the same sources as the Ontario review for relevant studies. These include the International Network of Agencies for Health Technology Assessment (INAHTA) database of HTAs,[38] and a targeted grey literature search of systematic review registries and HTA agency websites. Unlike the Ontario Review, the NHS Economic Evaluation Database will not be examined, as no new records have been added to this database since 31 March 2015 (which means that all relevant records on this database will have been captured in the original Ontario review).[39] A specific search of clinical trial registries will not be conducted, given that clinicaltrials.gov records are now included in the search of the Embase via Ovid database.[40]

Study selection

With respect to the search for additional studies, titles and abstracts will be screened by a single reviewer. The full texts of potentially eligible studies will be retrieved and independently assessed for eligibility by two reviewers according to the criteria outlined in Table 1, with any disagreements being resolved by discussion or a third reviewer, if required. Screening will be undertaken using Covidence software.

5.2.4 Data extraction and management

Data extraction will be performed by one reviewer using Microsoft Excel software. All data extracted will be reviewed by a second reviewer, with disagreements resolved by discussion. A standardised data extraction template based on the tables reported in the Ontario Health review will be developed prior to undertaking the review. Examples of relevant data that will be extracted include study design, participant characteristics, description of intervention and comparator screening methods, and study outcomes.

Critical appraisal of evidence

The methodological quality of included systematic reviews will be assessed using the AMSTAR-2 tool. For randomised controlled trials, the Ontario Review assessed the risk of bias using the Cochrane Risk of Bias 2 tool.[41] For non-randomised studies, the Risk of Bias Assessment Tool for Nonrandomised studies was used.[42] For consistency, the present review will adopt the same approach. Each study will be assessed by one reviewer, with the assessment cross-checked by a second reviewer.

The quality of evidence for the pivotal outcomes (breast cancer mortality, cancer detection rate, recall rate, and interval cancer rate) will be evaluated using the GRADE (grading of recommendations, assessment, development and evaluation) approach.[43] Using this approach, the overall certainty in the evidence will be assessed based on the following considerations: risk of bias, inconsistency, indirectness, imprecision and publication bias.

The same version of GRADE will be used for the update as was used for the original review.[34]

Data synthesis

Due to heterogeneity in study populations, imaging processes and methods, the Ontario Health review did not include a quantitative synthesis of the available evidence. It is expected that the updated evidence will follow a similar pattern. Therefore, results will be synthesised narratively.

5.3 Clinical effectiveness and safety of substitution from digital mammography to alternative screening modality

While the primary focus of the literature has been on supplemental screening, once a person has been identified as having dense breasts, an alternative approach is to replace digital mammography with an alternative imaging modality in subsequent screening rounds. Expert opinion, provided by BreastCheck radiologists consulted during the development of this protocol, considered that only substitution to an alternative mammography-based method should be examined. Mammography is the current cornerstone of screening, is required to measure breast density, and can identify features such as calcifications that may not be identified with alternative imaging methods. Therefore, this chapter's analysis of substitution of screening modalities will be limited to CEM and DBT only.

Given the primary focus on supplemental screening in the literature, a narrative review outlining the clinical effectiveness and safety of substitution to CEM or DBT from digital mammography will be conducted. Outcomes considered will be in line with those defined for the clinical effectiveness and safety of supplemental screening (section 5.1.2), where available.

6. Ethical, patient, and social considerations

This chapter will aim to identify key ethical, patient, and social considerations regarding a modification of the BreastCheck programme to incorporate breast density notification with or without supplemental (or substitution) screening. This analysis will consider the wider implications of this modification for individuals with dense breasts, the general public, and the healthcare system in Ireland. A review of relevant Irish and international literature will be undertaken. This will be supplemented with an ethics workshop, at which members of the evaluation team will discuss these key considerations. Guided by the ethical analysis and patient and social domains of the EUnetHTA HTA Core Model®,[44] this chapter will examine potential ethical, patient, and social considerations relating to:

- **Balancing potential benefits and harms:** Notifying participants about their breast density and providing additional or alternative screening for those with dense breasts may lead to improved outcomes.[34] However, potential harms include false positives, unnecessary further investigations, psychological harms, and overdiagnosis and overtreatment.[34, 45] Breast density notification may also have benefits and harms for those without dense breasts. For example, this would apply in circumstances where participants

specifically receive a notification that they do not have dense breasts and where this influences their future screening participation behaviour.

- **Equity and access:** The addition of screening pathways that incorporate breast density could exacerbate existing inequities and barriers to accessing breast screening services in Ireland.[46, 47] This may be especially relevant for certain vulnerable groups, such as those of a lower socioeconomic status.[48]

- **Informed consent and shared decision-making:** It is important that any notification of breast density and consideration of modified screening pathways is based on prior informed consent that explains the associated potential benefits, harms and limitations.[34, 49]

- **Resource allocation:** The introduction of a screening pathway that considers breast density would place additional pressure on screening infrastructure and capacity, financial resources, and workforce.[34, 48] This may, in turn, negatively impact the delivery of other healthcare services and reduce the quality of care for people with symptomatic conditions.[7] As such, it is necessary to consider the ethical implications of the impact that modifications to the BreastCheck screening pathway may have on existing symptomatic services. The impact from an operational perspective (for example, the need to develop new IT and communication processes to allow the modified pathway to function appropriately) would be examined in more detail if this assessment progresses to the second phase.

7. Anticipated timeline

The draft report will be circulated and reviewed at meetings of the EAG. Necessary amendments and revisions will be made following these meetings before the assessment is submitted to the CEO of HIQA for approval. Subject to its approval, the report will be submitted to NSAC for consideration (expected delivery Q2 2026). Contingent on the findings of phase one, a second phase of work may be undertaken to assess the economic and organisational implications of incorporating breast density within the BreastCheck pathway.

8. References

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Appendix

Table A.1 NSAC criteria by HTA domain

Criterion No.	NSAC Grouping	Criterion	HTA domain(s)*
1	The Condition	The condition should be an important health problem. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease.	Epidemiology
2		All the cost-effective primary prevention interventions should have been implemented as far as practicable.	Not applicable**
3		If the carriers of a mutation are identified as a result of screening, the natural history of people with this status should be understood. The psychological implications should be considered, and the necessary psychological supports should be in place.	Epidemiology, ethical, social and legal issues
4	The Screening Method	The screening method should be, as far as is practicable: a) simple b) safe c) precise d) reliable e) validated.	Clinical effectiveness and safety, organisational issues
5		The distribution of screening values in the target population should be assessed and suitable cut-off levels/measurements defined and agreed by the applicant.	Description of technology, clinical effectiveness and safety, organisational issues
6		The screening process should be acceptable to the target population.	Ethical, social and legal issues
7		There should be an agreed policy on the further diagnostic investigation of individuals with a positive screening result and on the choices available to those individuals.	Description of technology, organisational issues
8		If screening is for a particular mutation(s) or set of genetic variants, the method for their selection should be kept under review.	Organisational issues

Criterion No.	NSAC Grouping	Criterion	HTA domain(s)*
9	The Intervention	There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care.	Description of technology, clinical effectiveness and safety
10		There should be agreed evidence-based policies covering which individuals should be offered interventions and the appropriate intervention to be offered.	Description of technology, organisational issues
11	The Screening Programme	Ideally there should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an informed choice, there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.	Clinical effectiveness and safety, ethical, social and legal issues
12		There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is acceptable and can be implemented.	Ethical, social and legal issues, organisational issues
13		The benefit gained by populations and individuals from the screening programme should outweigh the harms. The public should be informed of these harms and of their associated undesirable physical and psychological consequences.	Ethical, social and legal issues, organisational issues
14		The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (value for money). Assessment against these criteria should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource.	Economic analysis
15	Implementation Criteria	Clinical management of the condition and patient outcomes should be in place before a screening programme is initiated.	Organisational issues
16		Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme.	Organisational issues
17		All other options for managing the condition should have been considered (such as improving treatment or providing other services), to ensure that no more cost-effective intervention could be introduced, or current interventions increased within the resources available.	Economic analysis, ethical, social and legal issues

Criterion No.	NSAC Grouping	Criterion	HTA domain(s)*
18		There should be a plan for managing and monitoring the screening programme against an agreed set of quality assurance standards. This should include monitoring performance against different sub-groupings in the population.	Organisational issues
19		The potential benefits and harms of screening, investigation, preventative intervention or treatment, should be made available and explained to the eligible participants to assist them in making an informed choice. There should be a clear system of communication incorporated into each screening programme to ensure patients are kept aware of any developments in their case.	Ethical, social and legal issues, organisational issues
20		Decisions about commencing, expanding or ceasing a programme should be based on scientifically validated evidence.	All

Key: HTA – health technology assessment; NSAC – National Screening Advisory Committee.
Source of NSAC criteria: Department of Health.[50]
* A mapping exercise was conducted by the HIQA evaluation team to identify the relevant HTA domain for each of the individual NSAC criteria, based on the HTA Core Model® proposed by the European Network for Health Technology Assessment (EUnetHTA).[44] The mapping exercise aimed to clarify the extent to which a typical HTA addresses the NSAC criteria, and which HTA domain addresses which criterion/criteria.
** Considered outside the scope of a conventional HTA, unless the HTA is undertaken specifically to inform this criterion.

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