Title of the project

Risk-adapted breast imaging in population breast cancer screening programmes

Evidence Synthesis Group

Aberdeen Belfast Evidence Collaboration (ABEC)

Project lead

Miriam Brazzelli

Health Services Research Unit

University of Aberdeen

Health Sciences Building

Foresterhill,

Aberdeen AB25 2ZD

Email: m.brazzelli@abdn.ac.uk

Deputy lead

Sinead Duggan

Centre for Public Health

Institute of Clinical Sciences

Queen's University Belfast

Belfast BT12 6BA

Email: s.duggan@qub.ac.uk

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Other members of the ABEC project team (in alphabetical order)

Mohammad Azharuddin, University of Aberdeen

Mike Clarke, Queen's University Belfast

Rodolfo Hernandez, University of Aberdeen

Paul Manson, University of Aberdeen

Craig Ramsay, University of Aberdeen

Clare Robertson, University of Aberdeen

Graham Scotland, University of Aberdeen

Shaun Treweek, University of Aberdeen

Gianni Virgili, Queen's University Belfast

Relevant Stakeholders

UK National Screening Committee

Background and definition of the decision problem

Breast cancer

In the UK, breast cancer is the most common type of cancer among women, accounting for 15% of all new cancer cases. Based on data from 2016-2018[1] there are around 55,900 new breast cancer cases in the UK annually, corresponding to more than 150 per day. Whilst breast cancer can occur at any age, it most commonly affects women who are over the age of 50 years and have reached menopause.

Standard breast cancer screening in the UK

The UK breast cancer screening programme currently screens all women aged 50-70 years at three-year intervals with digital mammography (images of each breast from two views). Screening allows for the early detection of breast cancer which reduces cancer-related burden and mortality.[2-4] Although breast cancer screening is highly successful in preventing breast cancer mortality (20-40% reduction in risk)[3 5] death due to breast cancer is still not prevented in a substantial proportion of women due to underdiagnosis.[6] The current screening pathway is illustrated in Figure 1.

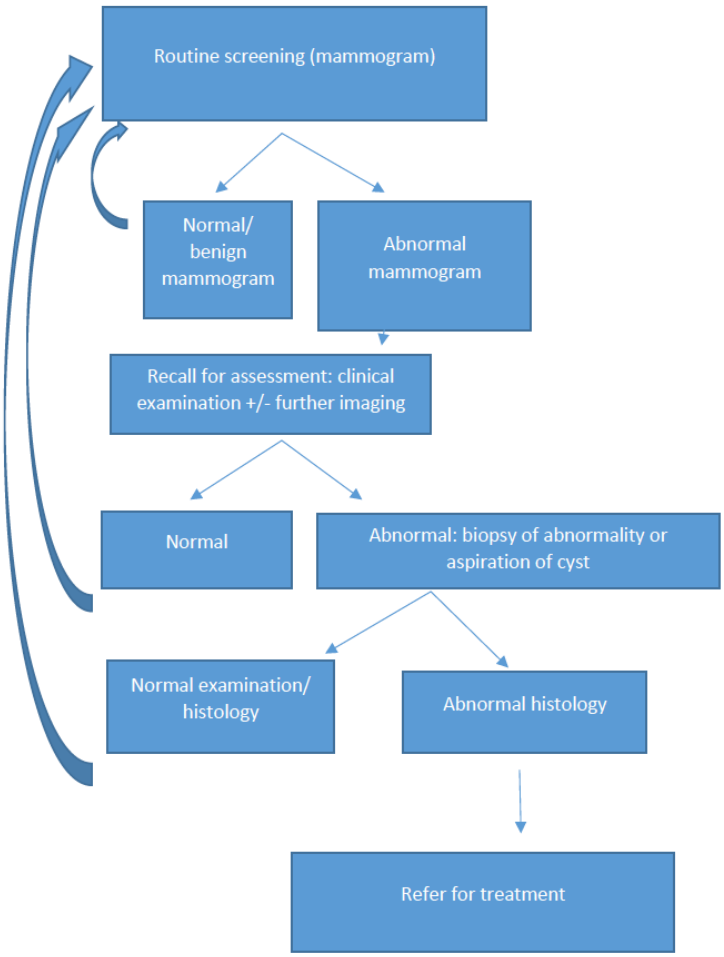

Figure 1

Current Pathway for Breast Cancer Screening in the UK[7]

Breast density and risk of breast cancer

Breasts contain glandular tissue, fibrous connective tissue, and adipose tissue. Breast density describes the relative amount of these various types of tissue as seen on a mammogram, specifically the proportion of radiologically dense fibro-glandular tissue relative to radiolucent adipose tissue on radiographic imaging. The distribution of the individual amount of fibroglandular tissue, and thus of mammographic densities across the female population, follows a typical Gaussian distribution of many biological features[8]. In clinical practice, this biologic continuum is categorised into four groups according to the American College of Radiology Breast Imaging Reporting and Data System (ACR BI-RADS) atlas [9 10] (Table 1). The Estimated percentage of the screening population refers to a US-based population (69% non-Hispanic white; 12% black; 11% Asian/Pacific Islander, 6% Latina, 2% multiple/other).[11]

Table 1 BI-RADS categorisation and proportion of population affected

BI-RADS Group	Description	Estimated % of screening population[11]
A	The breasts are almost entirely fatty	10
B	There are scattered areas of fibroglandular density	42
C	The breasts are heterogeneously dense, which may obscure small masses	40
D	The breasts are extremely dense, which lowers the sensitivity of mammography	8

Source: BI-RADS Breast Imaging Reporting and Data System [9,10]

In the context of screening, breast density is of concern for two reasons:

- Women with high breast density have an increased risk of breast cancer than those with low breast density. A systematic review (2022)[10] reported that having BI-RADS density D resulted in a 2.11-fold (95% CI 1.84–2.42) increased breast cancer risk compared to having BI-RADS density B, and a 3.89-fold (95% CI 2.47–6.13) increased breast cancer risk compared to having BI-RADS density A.
- The sensitivity of mammography screening is lower in women with more dense breasts.[12]

Women with extremely dense breasts (BI-RADS group D) and those with moderately dense breasts (BI-RADS group C) are, therefore, at risk of underdiagnosis. Together these two groups (BI-RADS C and D) may account for almost half of the screening population.[11] Earlier identification of breast cancer through supplemental screening modalities for women with dense breasts would allow for earlier intervention and better clinical outcomes. A risk-adapted screening protocol, wherein women

with dense breasts are offered supplemental or enhanced screening modalities, is increasingly being considered.

Risk-adapted screening: current UK position

In 2019, the National Screening Committee commissioned a report[7] on whether additional screening with ultrasound after negative standard mammography in women with breast density would be beneficial. The following questions were addressed:

Q 1 What are the reliability and concordance of available methods to measure mammographic breast density?
Q 2a: Is mammographic breast density a risk factor for cancers being missed during screening (masking on mammograms/false negatives/interval cancers)?
Q 2b: Is mammographic breast density a risk factor for developing breast cancer?
Q 3: What is the test accuracy of ultrasound following mammography in comparison to mammography to detect cancer in women with dense breasts?
Q 4: For women attending breast screening in the UK, what are the cost-consequences of adding mammographic density measurements, and then ultrasound for those found to have high mammographic breast density?

These questions were designed to fulfil specific National Screening Committee criteria:

- There should be robust evidence about the association between the risk of disease marker and serious or treatable disease (Criterion 1).
- There should be a simple, safe, precise and validated screening tool (Criterion 4).
- The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced concerning expenditure on medical care as a whole (value for money). Assessment against this criterion should have regard to evidence from cost-benefit and/or cost-effectiveness analyses and have regard to the effective use of available resources (Criterion 14).

Whilst the Committee found that there were consistent findings of reduced sensitivity of mammography and increased risk of interval cancers with increasing mammographic breast density, they pointed out that it was difficult to validate the methods for measuring breast density, and that ultrasound led to large numbers of false positive cases. In addition, the report showed that there was no evidence as to whether ultrasound reduced either interval cancers or mortality and to what extent identification of additional cancers represented overdiagnosis. The report also stated that the limited cost-effectiveness evidence suggests that supplemental ultrasound is not currently cost-effective.

Based on these findings, the Committee decided against the need for additional ultrasound screening after negative mammography in women with breast density.[7]

Imaging modalities for the detection of breast cancer in women with dense breasts

Aside from standard mammography, several other imaging modalities may be used to detect breast cancer in women with breast density. These include magnetic resonance imaging, ultrasonography (using either hand-held or automated modalities), contrast-enhanced mammography, and digital breast tomosynthesis.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) of the breast is a technique that uses magnetic fields and radio waves to create detailed images of the breast. A standard dose of gadolinium-containing contrast agent is administrated during MRI examination. Tumour-associated blood vessels have increased vascular permeability which is responsible for the uptake and washout of gadolinium after its administration. The morphology of the lesions, the enhancement and washout kinetics help distinguish pathological from benign lesions.[13] Full MRI or abbreviated MRI examinations can be used for breast cancer screening. Abbreviated MRI is a shorter version of the standard breast MRI, which produces fewer images and requires less time.

Breast hand-held ultrasound

Hand-held breast ultrasound (HHUS) is a non-invasive technique that uses waves to capture images of areas of the breast that may be difficult to see with mammography. It has been used for diagnosing breast cancer since the 1970s. It can help delineate morphological characteristics and internal structures and measure breast abnormalities in women with breast density but is susceptible to false positive results.

Automated breast ultrasound

Automated breast ultrasound (ABUS) is a specifically designed ultrasound machine for the assessment of breast-dense tissue. It has been developed to overcome the limitations of hand-held ultrasound in terms of operator dependency and poor reproducibility. [14]

Contrast-enhanced mammography

Contrast-enhanced mammography (CEM) is an emerging technique that uses intravenous injection of a dye containing iodine in combination with a standard digital mammogram. The iodine contrast agent is the same as that used for computed tomography scans but different from the gadolinium-based agent used for MRI. CEM can allow a malignant tumour to be seen despite overlying dense breast tissue.[15]

Digital Breast Tomosynthesis

Digital breast tomosynthesis (DBT) is an advanced form of mammography that uses a low-dose x-ray system and computer reconstructions to create images of the breasts. It is sometimes referred to as '3D mammography'; however, the images are not truly three-dimensional.[16]

Breast density and ethnicity

Breast density in women appears to vary by ethnicity. Whilst breast cancer incidence rates have been traditionally lower in Eastern countries, rates are rapidly rising - potentially attributable to increased obesity, reduced physical activity, and decreased reproduction.[17] Breast cancer is the highest incidence of malignancy in Japanese women. The Japanese Breast Screening Programme includes women in their 40s and has no upper age limit. Although breast cancer mortality rates have been declining in developed Western countries in the early 1990s attributable to screening programmes, the implementation of screening programmes in Japan has not been associated with a reduction in mortality rates.[18] This could be due to underdiagnosis with standard mammography as Japanese women typically have more dense breasts than women in Western countries.[17] A study published in 2019 that compared breast density among Australian and Japanese women found that 90% of Japanese women in the 40-49 year age group (this group have the highest incidence of breast cancer in Japan)[19] had extremely dense breasts compared with 38% of Australian women in the same age group.[20]

Recent changes to international screening programmes

Global policies on supplemental screening modalities for women with dense breasts have been broadly consistent with the UK position. However, in the last 1-2 years, several groups have recommended changes to their policies regarding informing women of their density status, or enhanced screening (see Table 2). However, new recommendations are not consistent across policies.

In 2022 the European Commission Initiative on Breast Cancer, which does not endorse the use of MRI or ultrasound, recommended the use of DBT in women with breast density detected in previous screenings.[21] In the same year, the European Society of Breast Imaging recommended supplemental screening every 2-4 years in women with extremely dense breasts, preferably with MRI.[22]

In 2020, Breast Screen Australia advised against recording breast density and performing supplemental screening.[23] However, later in 2023, the Royal Australia and New Zealand College of Radiologists recommended the reporting of breast density in both screening and diagnostic settings.[24]

The Canadian Task Force of Preventative Health, which in 2018 did not specifically review the evidence for additional breast cancer screening for women with dense breasts, is now updating their recommendations that will be released in 2024.

Similarly, the United States Preventive Services Task Force in 2016 decided there was insufficient evidence to assess the benefits and harms of enhanced screening for breast cancer using supplemental modalities,[25] are currently updating their guidelines.[26] The Practice Advisory issued in March 2023 by the United States (US) Food and Drug Administration (FDA) requires disclosure of a patient's breast density as recorded in the mammogram report to clinicians (based on the 4-category BI-RADS classification) and in the patient' lay summary (as a binary classification: 'dense' or 'not dense').[27] Effective from September 2024, letters to patients will need to inform women whether their breasts are dense or not dense and that additional screening may help to detect cancer. Thirty-eight US states, and the District of Columbia (DC) have dense breast notification laws that mandate varying levels of patient notification about breast density following a mammogram, covering more than 90% of American women.[28] The American College of Gynaecologists has also enforced the FDA Practice Advisory position.

Table 2 Summary of international guidelines and recommendations regarding enhanced screening of women with breast density

Location	Authority/Institution	Date	Recommendation	Additional information
Europe	European Commission Initiative on Breast Cancer[21]	2017-21	For asymptomatic women with high mammographic breast density detected for the first time, the committee suggested not implementing tailored screening with additional DBT, MRI, ABUS or HHUS.	The committee suggested using DBT for women with high mammographic breast density detected in previous screening exams.
	European Society of Breast Imaging	2022	Supplemental screening every 2-4 years for women with extremely dense breasts, preferably with MRI.	

USA	United States Preventive Services Task Force[25]	2016	Insufficient evidence to assess the balance of benefits and harms of enhanced breast screening.	Update in process (as of January 2024).[26]
	American College of Gynaecologists[29]	2016	Routine use of adjunctive breast screening modalities is not recommended due to the lack of evidence.	Update March 2023: Endorse compliance with the FDA Practice Advisory that requires disclosure of breast density based on mammographic findings to clinicians and patients.[27]
Canada	Canadian Task Force on Preventive Health Care[30]	2018	The task force did not specifically review evidence on supplemental screening for women with dense breast tissue	Updated Guidelines are expected in Spring 2024.
Australia and New Zealand	Breast Screen Australia Programme[23]	2020	Position Statement: Standing Committee on screening recommends that until more evidence is available, BreastScreen Australia should not routinely record breast density or provide supplemental testing for women with dense breasts.	The December 2023 Position Statement of the Royal Australia and New Zealand College of Radiologists [24] recommends the reporting of breast density in both screening and diagnostic settings.

Keys: *FDA, Food and Drug Administration; DBT, Digital breast tomosynthesis; MRI, Magnetic Resonance imaging; ABUS, Automated Breast Ultrasound; HHUS, hand-held ultrasound.*

The BRAID Trial

In the UK, it is anticipated that results from the multicentre Breast Screening - Risk Adapted Imaging for Density (BRAID) trial will be published at the end of 2024.[31] This trial is investigating the ability of supplemental screening modalities (abbreviated MRI, ABUS, CEM) to detect additional breast cancer cases in women with dense breasts (BI-RAD categories D and C).

Key factors to be addressed

To support decision-making about the current UK breast screening programme, we aim to address the following research questions.

Research question 1:

What is the agreement between automated and manual measurements of mammographic breast density?

Research question 2:

What is the effect of supplement imaging screening compared with standard screening for identifying breast cancer in women with dense breasts?

Research question 3:

Has the cost-effectiveness of supplemental breast cancer screening in women with dense breasts been explored in high-quality modelling studies?

The main objectives of this assessment are the following:

- To determine the performance of automated versus manual methods for the assessment of breast density.

- To determine the breast cancer screening performance of supplemental imaging modalities for women with dense breasts at risk of breast cancer.

- To review evidence on existing economic models assessing the costs and consequences of enhanced mammographic screening for women with dense breasts.

Evidence synthesis methods

Target population

Our population of interest is women between 40 and 70 years of age undergoing screening. However, we will accept the age range reported by the authors of the included studies. We will consider equity, diversity and inclusion aspects in the conduct of this evidence synthesis and when possible, we will summarise the characteristics of participants from the included studies using the PRO EDI participant table.[32] When possible, we will consider subgroup analyses according to age groups.

Study design and outcomes of interest

The type of studies and relevant clinical outcomes considered appropriate to address the objectives of this evidence synthesis are shown in Tables 2-4 below.

Table 2 Eligibility criteria for research question 1 (agreement between automated and manual measurements of breast density)

Population	**Women between 40 and 70 years of age undergoing breast cancer screening**
Intervention: Automated methods for measuring breast density	Semi-automated and fully automated methods will be deemed suitable for inclusion. We will exclude methods of measuring risk from AI technologies applied to mammograms that are not based on breast density. Semi-automated methods may include Cumulus, ImageJ-based method or DM-scan. Fully automated methods may include Densitas, DM-scan, LIBRA, Quantra, SXA, or Volpara.
Comparator intervention: Manual methods for measuring breast density	Manual (visual) measurement of breast density (% density or BI-RADS classification edition 3, 4 or 5). To be eligible for inclusion studies must compare a semi-automated or fully automated method for measuring breast density with a manual measurement.
Outcomes	Measures for consideration may include: • Agreement between manual and automated methods for measuring breast density • Resources needed to measure breast density (number and experience of health professionals performing the measurement)
Study design	We will focus on studies published in English in the last 10 years that assess the agreement between measurements obtained using a semi-automated or fully automated method with those obtained from a manual measurement. Conference abstracts will be excluded because they are not considered to provide sufficient information. However, if potentially relevant conference abstracts are identified, we will investigate whether fuller information is available from another source.
Healthcare setting	Breast cancer screening setting

Table 3 Eligibility criteria for research question 2 (enhanced mammographic screening for women with breast density)

Population	**Women between 40 and 70 years of age undergoing screening who have been stratified by breast density categories using either visual or automated methods**
Intervention	Supplemental imaging modalities for detection of breast cancer in women with breast density. These may include: Magnetic resonance imaging (full MRI/abbreviated MRI), Contrast-enhanced mammography (CEM) Ultrasound (hand-held HHUS/automated ABUS) Digital breast tomography (DBT)
Comparator intervention	Mammography We will not include articles that report direct comparisons of the diagnostic performance of mammography versus another imaging modality or articles that assess the diagnostic performance of single imaging modalities.
Outcomes	Relevant outcome measures may include: • Cancer detection rate • Interval cancer rate • Recall rate • Positive predictive values • False positive rate • Sensitivity • Specificity • Cancer stage and nodal involvement at detection • Time needed for the additional imaging modality to be performed
Study design	We will focus on primary studies published in English in the last 10 years that assess the performance of supplemental imaging modalities for the detection of breast cancer in women with breast density. Conference abstracts will be excluded because they are not considered to provide sufficient information. However, if potentially relevant conference abstracts are identified, we will investigate whether fuller information is available from another source.
Healthcare setting	Breast cancer screening setting

Table 4 Eligibility criteria for research question 3 (review of economic evaluations)

Population	**Women between 40 and 70 years of age undergoing screening who have been stratified by breast density categories using either visual or automated methods**
Intervention	Supplemental imaging modalities for detection of breast cancer in women with breast density. These may include: Magnetic resonance imaging (full MRI/abbreviated MRI), Contrast-enhanced mammography (CEM) Ultrasound (hand-held HHUS/automated ABUS) Digital breast tomography (DBT)
Comparator intervention	Mammography
Outcomes	Relevant outcome measures may include: • Medical resource use and costs • Life years/life years gained • Utilities and Quality Adjusted Life Years (QALYs) • Incremental cost-effectiveness ratio (ICER) per life year or quality-adjusted life year (QALY) • Net monetary benefit or net health benefit • Cost/accurate diagnosis • Cost/true positives
Study design	We will focus on primary economic evaluations published in English in the last 10 years that assess the costs and consequences of supplemental imaging modalities for the detection of breast cancer in women with breast density. Only full economic evaluations, comparing the costs and consequences of two alternative courses of action, will be included (i.e., cost-effectiveness, cost-utility, cost-benefit and cost-consequence analyses).
Healthcare setting	Breast cancer screening setting

Search methods for identification of reviews or studies

Comprehensive literature search strategies will be developed by an Information Specialist to identify relevant published peer-reviewed articles. Major electronic databases will be searched, including MEDLINE, Embase, Scopus, The Cochrane Database of Systematic Reviews, Web of Science, CENTRAL, the NHS Economic Evaluations Database, the HTA Database, Research Papers in Economics and the ISPOR Scientific Presentations Database. The searches will focus on imaging modalities to detect breast cancer in women with breast density and on manual and automated measurements of breast density. The search strategies will include both database index terms and text words. The reference lists of articles selected for full-text appraisal will be screened for additional sources of evidence. Ongoing trials will be identified by searching major clinical trial registries. The websites of relevant professional organisations and health technology agencies like NICE, Canada's Drug and Health Technology Agency (CADTH), the Pharmaceutical Benefits Advisory Committee (PBAC), and the Institute for Clinical and Economic Review (ICER) will be searched for additional reports. No language restrictions will be applied to the searches. Still, results will be limited to articles published within the last 10 years to capture modern imaging modalities for breast cancer and methods for measuring breast density. Existing systematic reviews will be used as a source of relevant primary studies but will not be updated. All identified references will be exported to Endnote for recording and deduplication. A draft MEDLINE search is detailed in Appendix 1.

Study selection and data extraction strategies

One reviewer will screen the citations identified by the search strategies. A second reviewer will independently screen a random sample of citations (20%). Potentially relevant articles will be retrieved in full and assessed independently by two reviewers according to the pre-specified inclusion criteria. Multiple publications of the same study will be linked and considered together. The number of excluded studies will be noted and the main reasons for exclusion documented. The study selection process will be depicted through a PRISMA flow diagram.

The following information will be recorded from the included studies:

- Characteristics of publication: first author, year of publication, geographical location, language, screening setting, objectives, inclusion and exclusion criteria.
- Characteristics of participants: age, ethnicity, history of cancer.
- Number and experience of the health professional involved in the measurement of breast density.
- Characteristics of relevant imaging modalities (MRI, CEM, HHUS, ABUS, DBT).
- Measures assessing agreement between manual and automated measurements (e.g., correlation and reliability measures) [research question 1].
- Screening accuracy outcomes (e.g., sensitivity and specificity and positive predictive values)

and screening efficacy measures (e.g., cancer detection rate, interval cancer rate, recall rate). [research question 2]

- Information pertinent to economic modelling and costs including economic model type, model structure, time horizon, discount rates, model validation, resource used and cost categories, quality of life/utilities, total costs and QALYs, incremental cost-effectiveness ratios [research question 3].

Data will be extracted by one reviewer using a bespoke data extraction form and verified by a second reviewer. Extracted data will be recorded using Microsoft Excel®.

Risk of bias assessment

According to the study design of the identified evidence, appropriate risk of bias tools will be used for this evidence synthesis. The QUADAS-2 criteria will be used to assess the risk of bias in imaging screening studies and the checklist developed by the HSRU, University of Aberdeen, in partnership with the NICE Review Body for Interventional Procedures (ReBIP) will be used to assess the methodological quality of non-randomised evidence reporting quantitative data on the methods for the measurement of breast density. The ReBIP checklist was adapted from several sources[33-36] and comprises 17 items, which assess the following aspects: generalisability, sample definition and selection, description of the intervention, outcome assessment, adequacy of follow-up, and performance of the analysis. The reporting of identified economic evaluations will be assessed using the Consolidated Health Economic Evaluation Reporting (CHEERS) checklist.[37] The quality of decision models will be critically appraised by assessing the appropriateness of the model structure and data input used (e.g., accuracy of imaging data, baseline data, treatment effects, utility weights, resources, and costs), as well as the way parameters have been incorporated in the decision model. The quality check will be guided by the criteria used in the Philips checklist for good practice in decision-analytic modelling in health technology assessment.[38]

Any disagreements between reviewers regarding study selection, data collection and risk of bias assessment will be resolved by consensus or referred to a third reviewer for arbitration.

Data synthesis

The findings of primary studies will be summarised narratively and, when appropriate, through meta-analyses. We expect studies to assess the agreement between automated and manual measurements of breast density using various statistical methods (e.g., Pearson's correlation coefficient, intraclass correlation coefficient, Cohen's kappa coefficient, Bland Altman plot). Data for each comparison

between specific automated methods and manual measurement will be tabulated and critically summarised.

For studies that compare the performance of supplemental imaging screening to standard mammography for dense breasts, we will follow the methods recommended by the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy and present the results for each screening modality (e.g. MRI, CEM, HHSU, ABUS, DBT) separately. When possible, according to the data reported in the primary studies, we will present pooled estimates with 95% CIs for accuracy (e.g., sensitivity and specificity, PPVs) and efficacy screening outcomes (e.g., detection rate, recall rate, interval cancer rate). Results of random-effects meta-analyses will be presented in summary tables and displayed graphically using forest plots. The width of the CIs will be used as a measure of the precision and reliability of the effect estimate.

The I^2 statistic will be used to describe the percentage of total variation across included studies due to heterogeneity rather than chance.[39] We will use the following thresholds for the interpretation of I^2: <30% will indicate low heterogeneity, 30–60% moderate heterogeneity and >60% substantial heterogeneity.[40]

Findings of the economic evaluations will be tabulated and summarised using a narrative synthesis. Specifically, we will assess the transferability of the results of decision-analytic models to the UK decision-making context using the NICE reference case.[41]

We will use the STATA software (version 18 or the latest version, StataCorp, College Station, Texas) for all statistical analyses.

Studies Within a Review (SWAR)

We will embed versions of two SWARs in this evidence synthesis project. We will conduct a version of SWAR 06 as an observational study of the time taken to complete the various tasks of the review process, including study selection, data extraction, risk of bias assessment and analysis. Furthermore, when the review is finished, we will consider conducting a version of SWAR 02, which would compare user understanding of different types of summaries of the review and its findings (e.g. plain language summary, scientific abstract and podcast).

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Appendix 1 Search Strategies

Draft MEDLINE search for research question 1 (agreement between automated and manual measurements of breast density)

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions 1946 to present

1. breast density/
2. ((breast or mammograph*) adj5 dens*).tw,kf.
3. 1 or 2
4. (automat* or "semi-automat*" or "computer-assist*" or objective or quantitative).tw,kf.
5. (Cumulus or ImageJ or "DM-scan" or Densitas or LIBRA or Quantra or SXA or Volpara).tw,kf.
6. Radiographic Image Interpretation, Computer-Assisted/
7. 4 or 5 or 6
8. (manual or visual or radiologist? or reader?).tw,kf.
9. (concordance or agreement or compar* or correlat* or kappa or "Bland-Altman" or "reference standard" or "gold standard").tw,kf.
10. 3 and 7 and 8 and 9
11. limit 10 to yr="2014 -Current"

Draft MEDLINE search for research question 2 (enhanced mammographic screening for women with breast density)

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions 1946 to present

1 Mass Screening/ or Early Detection of Cancer/

2 Breast/ or breast?.tw.

3 1 and 2

4 (breast adj3 (screen* or imag*)).tw,kf.

5 3 or 4

6 breast density/

7 ((breast? or mammog*) adj5 dens*).tw,kf.

8 6 or 7

9 *Mammography/ or mammogra*.tw,kf.

10 *Magnetic Resonance Imaging/ or ("magnetic resonance imaging" or MRI).tw,kf.

11 *Ultrasonography, Mammary/ or (sonogra* or ultrasound* or ultrasonogra* or echomammogra* or ABUS or HHUS).tw,kf.

12 (("contrast-enhanced" adj3 mammogra*) or CEM).tw,kf.

13 (tomosynthesis or "3D mammogra*" or "3-D mammogra*" or "digital breast tomogra*" or DBT).tw,kf.

14 ((supplement* or enhance* or adjunct* or addit* or "risk-adapted" or "risk adapted") adj5 (screen* or imag*)).tw,kf.

15 or/10-14

16 ("cancer detection rate?" or CDR or "screen detected cancer?" or "interval cancer?" or (cancer? adj3 missed) or (cancer? adj3 detect*)).tw.

17 ((additional or differen* or increas* or improv*) adj3 (yield? or cancer? or detect*)).tw.

18 16 or 17

19 5 and 8 and 9 and 15 and 18

20 (case reports or comment or editorial or letter or news).pt.

21 19 not 20

22 limit 21 to yr="2014 -Current"

Draft MEDLINE search for research question 3 (systematic review of economic evaluations)

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions 1946 to present

1 Mass Screening/ or Early Detection of Cancer/

2 breast/ or breast?.tw.

3 1 and 2

4 exp Breast Neoplasms/

5 (breast adj3 (screen* or imag*)).tw,kf.

6 3 or 4 or 5

7 *Mammography/ or mammogra*.tw,kf.

8 *Magnetic Resonance Imaging/ or ("magnetic resonance imaging" or MRI).tw,kf.

9 *Ultrasonography, Mammary/ or (sonogra* or ultrasound* or ultrasonogra* or echomammogra* or ABUS or HHUS).tw,kf.

10 (("contrast-enhanced" adj3 mammogra*) or CEM).tw,kf.

11 (tomosynthesis or "3D mammogra*" or "3-D mammogra*" or "digital breast tomogra*" or DBT).tw,kf.

12 ((supplement* or enhance* or adjunct* or addit* or "risk-adapted" or "risk adapted") adj5 (screen* or imag*)).tw,kf.

13 7 or 8 or 9 or 10 or 11 or 12

14 *economics/

15 exp *"costs and cost analysis"/

16 (economic adj2 model*).mp.

17 (cost minimi* or cost-utilit* or health utilit* or economic evaluation* or economic review* or cost outcome or cost analys?s or economic analys?s or budget* impact analys?s).ti,ab,kf,kw.

18 (cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit or costs).ti,kf,kw.

19 (life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s).ab,kf,kw.

20 (cost or economic*).ti,kf,kw. and (costs or cost-effectiveness or markov).ab.

21 or/14-20

22 6 and 13 and 21

23 limit 22 to yr="2014 -Current"