A Technical Review of Breast Density Reporting in Cancer Screening

Te Kāwanatanga o Aotearoa
New Zealand Government

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Glossary and Abbreviations

AI	Artificial Intelligence
BC	Breast Cancer
BCSC	Breast Cancer Surveillance Consortium
Biopsy	Removal of a sample of tissue from the body for examination under a microscope by a pathologist to assist with the diagnosis of a disease.[1]
BI-RADS	American College of Radiology's Breast Imaging-Reporting and Data System. In clinical settings, breast density is typically evaluated using two-view mammograms and classified according to this system.
BMI	Body Mass Index
BOADICEA	Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm
BRCA	The two BRCA (BReast CAncer) genes (BRCA1 and BRCA2) are tumour suppressor genes that help prevent cancers from developing. There is a substantially higher risk of developing breast, ovarian, and other cancers in people who have inherited a mutation in either of these genes.2
BD	Breast density refers to the relative amount of fibrous and glandular tissue compared to fatty tissue that can be visualised and measured by breast mammography. This is not the same as physical firmness of breast tissue.
BSA	BreastScreen Aotearoa.
Cancer	A general term for a large number of diseases that all display uncontrolled growth and spread of abnormal cells. Also called a malignant tumour. Cancer cells have the ability to continue to grow, invade and destroy surrounding tissue, and leave the original site and travel via the lymph or blood systems to other parts of the body, where they may establish further cancerous tumours.[1]
CEM	Contrast-Enhanced Mammography – An imaging modality that may be used for breast cancer screening. Combines conventional mammography with iodinated contrast medium and involves an X-ray subtraction technique to improve cancer detection.[3]
Coverage	Is defined as the proportion of women eligible for screening who have been screened in the previous two-year period. The number of women eligible is derived from Statistics New Zealand Census base populations at the midpoint of the two-year screening period. It

	bases eligibility on age and does not account for those who may be otherwise ineligible, or who chose not to participate. It also does not include participants undertaking private mammography outside BSA. Therefore, the true participation rates and true overall mammography uptake are unknown.
Digital Breast Tomosynthesis (DBT)	An imaging modality that may be used for breast cancer screening. Uses multiple X-ray images to create a 3D breast image.[4]
False positive	A positive screening test in a person who does not have the condition being screened for. The higher the proportion of false positives, the more people are referred for unnecessary further assessment. A test with a false positive rate of 0% will mean that no one is referred for further assessment unnecessarily.[1]
False positive rate for screening mammograms	The proportion of women who do not have cancer but are given an abnormal mammogram result (false positives), calculated as the number of false positive results divided by the total number of women screened.[1]
False negative	A negative screening test in a person who does have the condition being screened for. People with false negative tests are falsely reassured that they do not have the disease in question, and as a result may delay seeking help if symptoms develop later.[1]
GP	General Practitioner
HNZ	Health New Zealand | Te Whatu Ora
IBIS	International Breast Cancer Intervention Study
Incremental cancer detection rate	The number of additional cancers detected at screening with a particular modality relative to another. This is often stated as a percentage of screens or as a rate per 1000 screens.[5]
Interval cancer	A cancer that is diagnosed between a negative screen and the time a next screen would have occurred. In Breast Screen Aotearoa, this is a cancer diagnosed within two years of a negative screen. [1]
Interval cancer rate	The number of interval cancers diagnosed in a given population during a given period of time. The interval cancer rate is usually expressed per 1000 people per year. The interval cancer rate should be calculated by 12-month intervals from the time of the last screen, and by using the entire time interval from the previous screening.[1]
Lifetime risk	The likelihood that a particular event will occur during a person's lifetime, for instance developing a particular type of cancer. [6] This

	may be expressed as the overall lifetime risk from birth, or the risk within the woman's remaining lifetime.
5-year risk of cancer	The likelihood that a person who is free of a certain type of cancer will develop that type of cancer within 5 years.
Lead Providers (LP)	Lead Providers are organisations that provide breast screening services for BreastScreen Aotearoa.[1]
Mammogram	A soft tissue X-ray of the breast, which may be used to evaluate a lump, or as a screening test in women with no signs or symptoms of breast cancer.[1]
MRI	Magnetic Resonance Imaging – An imaging technique that may be used for breast cancer screening. Uses magnetic and radiofrequency fields to produce 3D images. Breast screening using MRI requires intravenous contrast, but does not utilise ionising radiation (X-rays).[7]
Negative mammogram	A mammogram that has been classified as normal during a routine screening.[1]
NPHS	National Public Health Service
Overdiagnosis	The diagnosis of cancers that would never progress to cause symptoms and/or death during an individual's lifetime.[8]
PHA	Public Health Agency
Positive predictive value of screening mammogram	The proportion of people having the outcome in question (i.e. a cancer) if the screening test is abnormal, usually expressed as a percentage. The higher the positive predictive value, the more likely it is that the person has the outcome in question (i.e. a cancer) when their test is positive. A screening test with a high positive predictive value is beneficial, since it will reduce the proportion of people having unnecessary further investigations. It is calculated as: the number of women with cancer and an abnormal mammogram result, divided by the total number of women with an abnormal screening mammogram result both with and without cancer.[1]
Recall for further assessment	A recall for performance of an additional procedure to clarify a perceived abnormality detected at screening.[5]
Recall rate	The number of women recalled for further assessment as a proportion of all women who were screened.[5]
Relative risk	The likelihood of a particular event occurring in one group compared with the likelihood of the same event occurring in another group.[6]
Risk stratification	Risk stratification or risk-based screening involves using a risk assessment process to allocate individuals to different screening protocols on the basis of their risk of cancer.

Screening	The examination of asymptomatic people in order to classify them as likely or unlikely to have the disease that is the object of screening. The aim of screening is to detect disease before it is clinically apparent, and for this to improve the outcome for people with the disease.[1]
Sensitivity	The likelihood that a test will detect a cancer when one is present, The higher the sensitivity, the better the test is at detecting cancer. A test with a low sensitivity will miss a lot of cancers. A test with a sensitivity of 100% will detect all cancers present. It should be calculated for both the screening test alone and for the screening programme (ie, both screening and assessment).[1]
Specificity	The likelihood that a test will exclude a cancer when one is not present, calculated as the number with true negative screening results (Y) as a percentage of Y plus the number of false positive screening results. The higher the specificity, the better the test is at excluding cancers when they are not present. A test with a low specificity will mean that a lot of people are referred for further assessment unnecessarily. A test with a specificity of 100% will mean that no one is referred for further assessment unnecessarily.[1]
Supplemental screening	Imaging used in addition to standard screening pathways, for example, undertaking MRI in addition to mammography to improve breast cancer detection.
Surveillance	Surveillance is the monitoring of individuals considered at increased risk of a condition and is generally of smaller scale, but increased intensity compared with screening, which effectively identifies high-risk individuals from an average risk population. The differences between surveillance and screening may not be entirely distinct, and screening organisations should work closely with those undertaking surveillance.[9]
Technical recall	A repeat mammogram because of technical inadequacy of the screening mammogram.[5]
Underdiagnosis	The failure to detect a cancer that is present, for example due to errors in clinical interpretation or technical constraints. [10]
US	Ultrasound - an imaging modality that may be used for breast cancer screening. Uses soundwaves to image tissue, with no radiation or contrast required.[4]
Wāhine Māori	Māori women

Executive summary

Breast density has become an important consideration within population-based breast cancer screening programmes worldwide. The role of breast density reporting and whether supplemental (additional) screening, should (or can) be offered to women with very dense breasts in the public system, is currently being assessed. Women with higher breast density have an increased risk of developing breast cancer (two to five-fold) compared to those with low breast density and are more likely to have a diagnosis missed by mammography.

International data suggests that potentially half of the female population are affected by high breast density and 5-10% of women will have very high density. The publicly funded, national breast screening programme BreastScreen Aotearoa (BSA), does not currently measure or report breast density. The distribution of breast density in the Aotearoa New Zealand female population is relatively unknown, with measurement in an appropriate cohort required to accurately estimate the proportion of women with dense breasts.

Mammographic breast density refers to the relative amount of fibrous and glandular tissue compared to fatty tissue within the breast. Measurement can be assessed from mammographic images visually by a radiologist or through automated reporting software based on algorithms and artificial intelligence (AI).

Screening programmes that incorporate breast density reporting are increasing. It has been mandated in the United States of America, is reported in most Canadian territories and is recommended by the European Society of Breast Imaging (EUOSBI), with at least 9 European countries reporting breast density. New South Wales, Western and South Australia report breast density in their screening programmes, with the Royal Australian and New Zealand College of Radiologists (RANZCR) recommending “mandating the reporting of breast density in both screening and diagnostic settings” in December 2023.

Supplemental screening in the context of breast screening refers to imaging used in addition to standard screening protocols that is undertaken to improve breast cancer detection. Internationally and in Aotearoa, supplemental breast screening has been recommended for women deemed to be at high risk of developing breast cancer. However, there are no universally agreed guidelines on screening type or timing, and women with dense breasts alone are generally not considered to reach a high enough level of risk.

Supplemental screening options including Magnetic Resonance Imaging (MRI), ultrasound and contrast enhanced mammography (CEM) have been shown to increase the detection of cancer compared to standard mammography. All methods are associated with varying risks and benefits. MRI has the greatest sensitivity for detection but comes with an increased false positive rate and is a costly procedure. Ultrasound is not as sensitive as MRI and has a similar false positive rate, however, it is a less invasive and less costly procedure. CEM is nearly as effective as MRI for cancer detection, with less false positives and is a simpler, lower cost method, however, is not routinely available and like MRI, uses intravenous contrast dye.

Studies investigating supplemental screening for women with dense breasts have shown increased cancer detection rates, detection of cancers earlier and decreased rates of interval cancers, however, whether this results in any additional lives saved is currently unknown.

Patient information about breast density is becoming increasingly available. Online information generally outlines the facts of breast density measurement but lacks discussion on the harms and benefits. Countries that do report on breast density usually provide notifications directly to patients. Overseas evidence suggests that women want to know their breast density, although this can be associated with anxiety and does vary across populations and healthcare contexts.

Risk-based screening protocols use risk assessment to provide personalised screening pathways that vary depending on the identification of risk. Those deemed to be at high-risk may receive more or different interventions than those at low risk. Modelling data supports the use of risk-based breast cancer screening protocols, including risk assessment tools and screening technologies, to provide personalised screening protocols that use resources efficiently and improve programme outcomes.

There are various methods for breast cancer risk stratification, with a number of tools available utilising different criteria (personal risk factors, family history, genetic testing), of which 3 include breast density. Population-based clinical trials are underway that are designed to assess the benefits and harms of supplemental screening for women with dense or extremely dense breasts and to investigate risk based screening that includes reduced screening for some very low risk groups.

In Aotearoa New Zealand there is significant inequity in breast cancer outcomes and screening coverage by ethnicity, with Māori women particularly impacted. Breast density reporting is available to women who have health insurance or pay for screening out-of-pocket through private providers. Studies have shown that women with dense breasts do not receive the same outcome benefits from current breast screening programmes as those with less dense breasts. There are a number of ethical considerations with the topic of breast density; one key issue is that failing to address the increased risk of breast cancer in women with dense breasts may be creating and perpetuating inequities for these women.

Key Conclusions

Breast density is an independent risk factor for breast cancer development and increased breast density can make it more difficult to identify breast tumours by mammogram. As such density should be considered when evaluating a women’s risk of breast cancer.

Women with higher-than-average risk of breast cancer may benefit from supplemental breast screening, however, currently there is no consensus on how best to manage women with dense breasts.

These factors need to be assessed in the context of the current BreastScreen Aotearoa screening programme with further consideration of introducing risk-based screening in the future.

Incorporation of breast density notification into an existing screening programme is ethically complex. Issues to review include equitable care, patient autonomy, physician trust, duty of care and uncertainties relating to measurement and clinical management pathways for women with dense breasts.

Consideration needs to be given to the best way to measure breast density within the BSA programme, including the possible use of AI versus visual assessment by radiologists and what the additional costs for these would be. The prevalence of breast density amongst women in Aotearoa New Zealand needs to be ascertained to understand the potential programme impacts, benefits and costs, including the potential number of women who may be offered supplemental screening.

Further evidence from international trials is required regarding the impact of supplementary screening for women with high breast density on breast cancer outcomes (e.g. mortality) and to provide guidance on risk stratification options, screening modality and interval.

Aotearoa New Zealand specific cost-effectiveness modelling would greatly assist in providing information regarding health system and economic implications of various policy options, including alternate ways to achieve marginal improvements to breast cancer outcomes (e.g. alternate age ranges, modalities (e.g. Digital Breast Tomosynthesis (DBT)), screening intervals, and interventions to improve current programme participation).

The current BSA workforce capacity needs to be assessed with regards to BreastCare nurses and Medical Imaging Technologists (mammographers) potentially needing to explain breast density results and recommendations for supplemental screening with women. As does the funding and workforce enhancements that would be needed to undertake further ultrasound/screening assessments.

The capacity of the wider health system to fulfil supplementary ultrasound or MRI requirements also needs to be assessed. Currently, CEM is not routinely available in Aotearoa New Zealand and there is limited availability of DBT. If supplemental screening is not available to women with dense breasts through the public health system, it will not be accessible to many due to cost. This is likely to further disadvantage some groups of women already facing inequities, for example, wāhine Māori with dense breasts and those living in areas of socioeconomic disadvantage.

A more detailed assessment of whole system capacity issues and potential impacts on the BSA programme in the context of current projects and existing coverage inequities for Māori and Pacific women is also required. This knowledge is necessary to produce robust local guidelines and recommendations for women with dense breasts.

1 Introduction

Breast density has been increasingly recognised as a key consideration in breast cancer screening. There is clear evidence that high breast density is both an independent risk factor for breast cancer and reduces the sensitivity of mammography for screening. As a result, population-based screening programmes internationally have been assessing the role of breast density reporting in their programmes and whether additional screening or surveillance, should (or can) be offered to women with very dense breasts. These considerations have included risk stratification, programme and workforce issues but, importantly, the views of consumers themselves.

Currently, breast density is not measured or reported as part of the BreastScreen Aotearoa (BSA) programme. The National Public Health Service (NPHS) has identified breast density as a key topic requiring further in-depth consideration in the Aotearoa New Zealand context. To this end, a joint working group was established with members from across Health New Zealand | Te Whatu Ora (HNZ) and including Te Aho o te Kahu the Cancer Control Agency and the Public Health Agency (PHA) in Manatū Hauora. A number of literature reviews were undertaken to address questions and points of interest identified by the working group (further details in Appendices 13.2) with resulting summaries synthesised into this technical review.

2 Breast Screening in Aotearoa New Zealand

2.1 BreastScreen Aotearoa

Initiated in 1998, BreastScreen Aotearoa (BSA) is Aotearoa New Zealand's publicly funded, national breast screening programme that offers free mammography nationally for eligible women aged 45–69 years biennially. [1]

- On 1 October 2024, the eligible age range for BSA was extended in Nelson-Marlborough. Those in this region who turned 70 on or after 1 October 2024, and those who are 74 (before they turn 75) are now eligible. HNZ is aiming to progressively extend the age range for free breast screening across the rest of Aotearoa New Zealand from October 2025.
- Eligibility criteria include women who;
- have not had mammography within the previous 12 months,
- are not pregnant or breastfeeding,

- are free from breast cancer (women previously diagnosed with breast cancer are eligible for screening at least five years after diagnosis),
- are asymptomatic
- are eligible for public health services in Aotearoa New Zealand.

Individuals considered at increased risk for breast cancer compared with those of "average population risk", or who present with symptoms or signs of breast cancer are managed through pathways outside of the BSA programme.[1] High-risk people with BRCA mutations are discussed further in section 11.1.

In HNZ the NPHS is responsible for the national management and oversight of BSA, and its service providers. Te Aho o Te Kahu provides strategic leadership for cancer control in New Zealand and works closely with NPHS to support their programme. There are eight regional Lead Providers (LP) who provide breast screening services for BSA. This includes all steps along the screening pathway, workforce recruitment and retention, and quality assurance. In addition, there are eleven Screening Support Service Providers who work in partnership with Lead Providers in their districts to support services directly to priority population groups – identified as Māori, Pacific, under screened and unscreened women. Both service providers are accountable to the NPHS and are responsible for ensuring their services are delivered according to the BSA National Policy and Quality Standards.[1] Screening is provided at fixed and mobile sites with further assessment usually provided at centralised locations within each district.[1]

2.2 Breast Screening Pathway

The breast screening pathway is described in Figure 1. It has multiple steps, including:

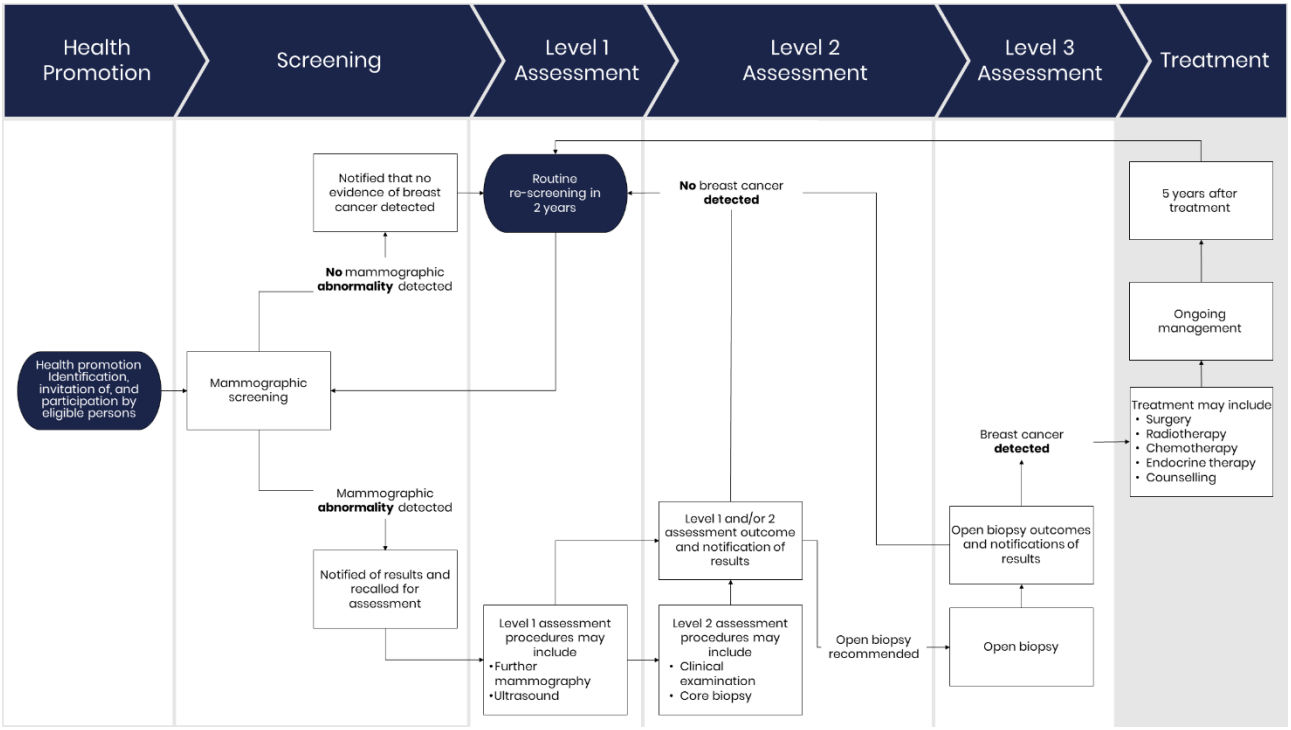
- Engagement with whānau, communities and service providers and screening promotion.
- Identification and enrolment of eligible women – historically, women were required to enrol themselves with BSA by telephone or online. In February 2025, a new system incorporating a population-based register was introduced that will invite women by email, text or letter to confirm enrolment and book appointments. The register is designed to capture a wider cohort of women and is estimated to reach an additional 135 000 participants.[11]
- Once enrolled, women are invited to an appointment for a mammogram at a local site and provided with support to access services where necessary.
- Screening mammograms are offered regionally at lead provider sites (fixed and mobile services).

- Mammograms are double-read independently by two accredited programme radiologists. Where there is discordance in these reads, a third read is undertaken. Artificial Intelligence (AI) is not currently used in the programme.
- For those with a negative mammogram (a mammogram that has been classified as normal during a routine screening, with no mammographic abnormality detected), a results letter will be sent to the individual and to their primary care provider (where consent for this has been given). These individuals will be recalled for routine screening in a further two years.
- If an abnormality is identified on mammography, the individual will be recalled for assessment.
- There are three levels of assessment testing where women may undergo some or all of the following procedures. Level 1. Further mammogram and/or ultrasound (US), Level 2. Clinical breast exam and/or needle biopsy (fine needle aspiration, core or vacuum assisted), Level 3. Excision or open surgical biopsy, or wire localisation open biopsy.
- If possible, provisional results will be given at the assessment otherwise final results are communicated after all clinical review processes are complete. If the result is no evidence of cancer, eligible women will be recalled to routine screening in a further two years.

Women with a diagnosis of cancer will be given counselling and information about treatment options and will be referred to a treatment service. After treatment for breast cancer, follow-up usually includes funded annual mammograms for five years. After five years, women are encouraged to re-enter the programme with BreastScreen Aotearoa for standard screening if still within the eligible age range. [1,12]

Note: Breast screening is available at private providers outside of BSA, however BSA does not have visibility/monitoring of mammograms taken outside of the programme.

Figure 1: BreastScreen Aotearoa screening pathway



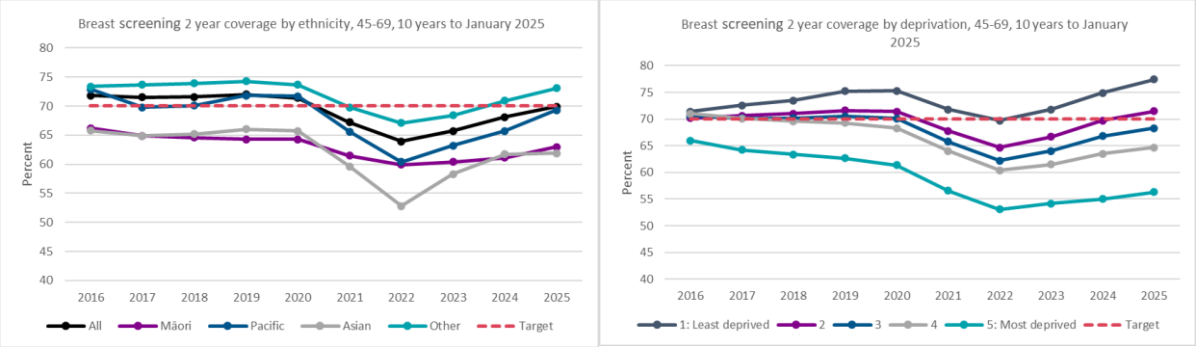
Source; Adapted from BreastScreen Aotearoa National Policy and Quality Standards 2013. Wellington: Ministry of Health.[1]

2.3 BreastScreen Aotearoa programme metrics

In a linkage study on the impact on mortality from breast screening in Aotearoa New Zealand, based on a participation rate of 71%, women who screened through BSA had a 34% reduction in mortality from breast cancer compared with women who did not screen after adjusting for age at death, ethnicity, and screening selection bias. This study demonstrated that mortality reduction was equitable for wāhine Māori and Pacific women compared with non-Māori, non-Pacific women, based on achieving specified participation rates.[13,14]

BSA screens approximately 270,000 women per annum with a target coverage rate of 70%. In the two years to January 2025, BSA screened 70% of the eligible population, with differing coverage rates by ethnicity and socioeconomic deprivation (see figure 2 below). Only 63% of eligible 45-69 year old wāhine Māori, 62% of Asian and 69% of Pacific women were screened compared to 73% of European/other women. Looking at coverage rate by deprivation status, only 56% of women living in the most deprived areas were screened compared to 77% of eligible women aged 45-69 years in the least deprived areas.[15] The COVID-19 pandemic had a significant impact on screening rates and inequities for Māori, Pacific and Asian women were exacerbated. Equity focused recovery plans are in place to address these as a priority.[16]

Figure 2: BSA screening coverage rates by ethnicity and deprivation



Data source: BreastScreen Aotearoa interactive coverage data tool accessed April 2025[15]

As per Figure 1, following mammography women are referred for assessment if there are concerns raised in the results. Nearly 10% (9.9%) of women aged 50-69 years having an initial screen and 3.5% of those having a subsequent screen through BSA were recalled for assessment in the two years to July 2022.[17] Of all women recalled for assessment, 12.8% of those following an initial screen and 18.8% following a subsequent screen were diagnosed with cancer (this is the positive predictive value – the number of women with cancer and an abnormal mammogram result, divided by the total number of women with an abnormal screening mammogram result both with and without cancer[1]). These figures vary by ethnicity, with the rates of referral for assessment and of cancer detection in those referred being higher for Māori and Pacific women. Of all the women screened aged 50-69 years, 7.3% of those having their initial and 2.6% of those having subsequent screens were recalled for assessment but did not have cancer (false positive rate).

In 2016 to 2017, for women aged 50-69 years, the interval cancer rate in the first 12 months after a screen was 6.3 per 10,000 women screened for initial screens and 5.1 per 10,000 women screened for subsequent screens. For the 12 to 24 months after a screen, the interval cancer rate was 14.5 per 10,000 women and 10.1 per 10,000 women for initial and subsequent screens.[18]

BSA monitor and report regularly on a range of clinical and programme indicators that are published on the Health New Zealand | Te Whatu Ora website (**BreastScreen Aotearoa programme monitoring reports – Health New Zealand | Te Whatu Ora**).

2.4 BreastScreen Aotearoa and Breast Density

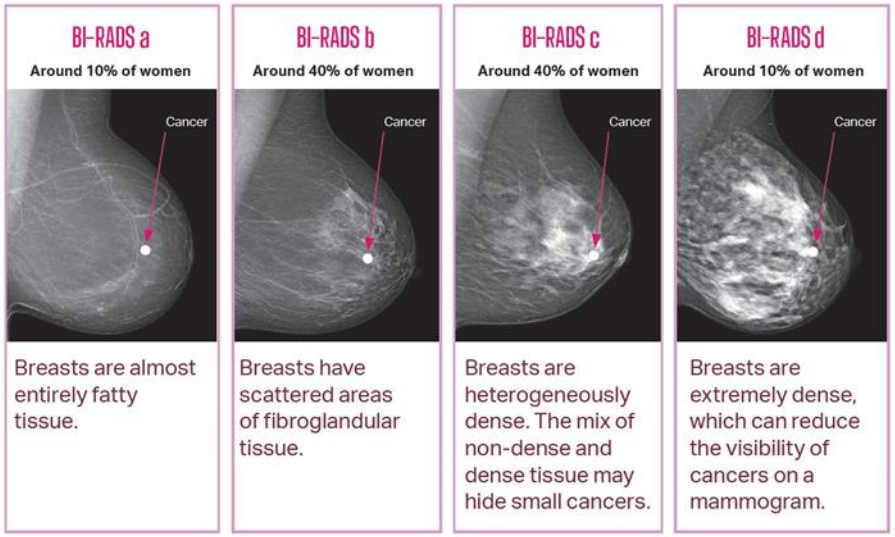
BSA does not currently measure, calculate or report breast density. BSA providers report that increasing numbers of participants are requesting their breast density information. A position statement on breast density was written and published on their website in 2019.[19] The evidence review at that time concluded that for women with dense breasts who otherwise have an average risk of breast cancer, there was insufficient evidence to recommend additional imaging. The position statement advises that women with dense

breasts at an otherwise average risk of breast cancer can be managed within BSA by regular mammography every two years. Women at high risk of breast cancer, for example those with very strong family history of breast cancer, or those with gene mutations, should be referred for additional care outside the BSA programme.

3 What is Breast Density

Breast density refers to the relative amount of fibrous and glandular tissue compared to fatty tissue that can be visualised and measured by breast mammography.[20,21] This is not the same as physical firmness of breast tissue. [22] Breast density is usually classified according to the American College of Radiology's Breast Imaging-Reporting and Data System (BI-RADS). The BI-RADS atlas provides standardised breast imaging terminology and a classification system for mammography, ultrasound and magnetic resonance imaging (MRI) of the breast. It includes a specific scale for breast density. This scale includes four categories, ranging from Category A (almost entirely fatty breasts), Category B (scattered areas of fibroglandular density), Category C (heterogeneously dense) to Category D (extremely dense breasts). Breast composition is defined by mammographic visually estimated content of fibroglandular-density tissue within the breasts and categorised accordingly. The female population distribution of 10% fatty, 40% scattered, 40% heterogeneous and 10% extremely dense breasts reflects the historical assignment from clinical practice and is due to the observation that a few coalescent areas of dense tissue may be present in breasts with as little as 10% dense tissue, whereas primarily fatty areas may be present in breasts with as much as 90% dense tissue. The fifth BI-RADS edition does not indicate ranges of percent dense tissue, instead it emphasises text descriptions which are currently believed to be more important clinically. This allows for subjective assessment of the volume of dense tissue and the relative possibility of masking, compromising the sensitivity of mammography. In the case of scattered density with a focally dense area, this may be categorised as heterogeneously dense. As the density category increases, the sensitivity for identification of non-calcified lesions decreases and larger lesions can be obscured. If breasts are not of apparently equal density the denser breast is used for categorisation. [23]

Figure 3: BI-RADS Classification of Breast Density



Source: Breast Screen South Australia[24]

Breast tissue density influences breast cancer management in two ways: firstly, high breast density is an independent risk factor for the development of breast cancer; secondly, high breast density can obscure potential lesions on mammograms, thereby reducing the diagnostic sensitivity of imaging tests. This masking effect makes it more challenging to detect tumours, as dense tissue and cancer both appear white on a mammogram, complicating the differentiation process.[25]

3.1 Breast density distribution in the population

Breast density is determined mainly by genetics and decreases with age, with a particularly marked decrease in density during menopause after which it stabilises.[26] It is also affected by factors such as parity, body mass index (BMI) and some medications e.g. menopausal hormone therapy and the oestrogen activity blocker tamoxifen. Breast density has been shown to decrease with increasing parity, increasing BMI and tamoxifen use, whereas breast density has been shown to increase with exposure to menopausal hormone therapies.[27–30] The association of these factors with density and risk of breast cancer development is further discussed in section 5.

Approximately 6-10% of women over the age of 40 have extremely dense breasts (equivalent to BI-RADS D category), and 40-45% have heterogeneously dense breasts (equivalent to BI-RADS C category). The remainder of women have fibroglandular or fatty breasts which are considered non-dense. [31–33]

Figure 4: Pictorial representation of the general population prevalence of breast tissue density for women

Ethnic differences in breast density are unclear, with unique patterns demonstrated across some ethnic groups in different screening populations[34–36]. A study in Aotearoa New Zealand conducted in the Northern Region, demonstrated that wāhine Māori (over 50 years) have higher absolute breast density and Asian women (all ages) have lower absolute breast density relative to New Zealand European/Other women. However, assessing volume percent breast density (the percentage of the total breast volume that is dense) there was no significant differences for wāhine Māori and Asian women had higher percent density compared to New Zealand European/Other. The sample contained fewer Māori and Pacific women and more Asian women than the general population at the time (2013) and there was a lack of additional data to assess the potential effects of confounding.[37] Further study is required to understand the true prevalence of breast density for Aotearoa New Zealand women.

It has also been suggested that there is a positive association between socioeconomic status and breast density, though this has largely been attributed to lower BMI in higher socioeconomic groups.[34,38,39]

4 Breast Density Measurement

4.1 Current State

In clinical settings, breast density is typically evaluated using two-view mammograms and classified according to the BI-RADS system described earlier. Mammographic visual assessment of breast density can be highly subjective and varies between observers as well as in the same observer over time. The highest discordance is between adjacent categories, more so between the least dense categories (A/B) than the high dense

categories (C/D).[40] This variability can lead to inconsistent diagnostic categorisation and treatment planning. Dual reading, where each mammogram is read by two radiologists can improve consistency and has been recommended.[41,42]

4.2 Artificial Intelligence

Artificial intelligence (AI) has been viewed as a potential solution to mammogram reader variability, providing more objective and standardised measurements, aiding clinical decision making. Historically, AI measurement was physics-based, calculating the total dense volume and total breast volume to provide volumetric percentage density. Two commercial companies, Volpara and Quantra, have pioneered and developed such algorithms which demonstrated fair to substantial agreement with BI-RADS reporting. With the advancements of AI in the early 2010s, a number of deep learning-based algorithms have been developed or incorporated into existing algorithms. These deep learning-based algorithms are capable of identifying intricate patterns in imaging data that are often not visible to the human eye and report improved accuracy over the previous physics-based algorithms from internal test results.[43,44]

The algorithmic-based approach to characterisation of breast density is not new, with many commercial products available. Figure 5 demonstrates the available algorithms and three broad approaches, either physics-based, machine learning-based or deep learning-based, described further below.[25]

Physics-based

The physics-based method relies on direct calculations derived from the properties of the breast tissues captured in mammograms. This approach involves measuring the total dense volume (fibroglandular tissue) and the total breast volume based upon different X-ray attenuation characteristics of fat, connective tissue and epithelial tissue of the breast. From these measurements, a volumetric percentage is calculated which correlates to the BI-RADS breast density classification. This method is grounded in physics, offering a systematic approach to assess breast density by quantifying the actual composition of the breast. [45]

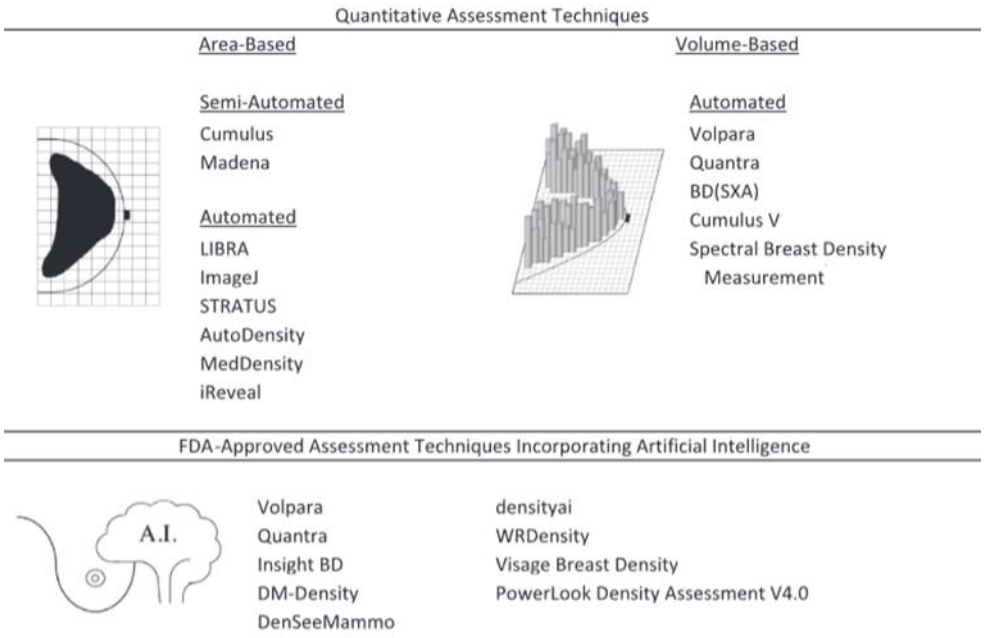
Machine learning-based

Limited information exists around the use of machine learning approaches for the classification of breast density. Quantra describes the use of a support vector machine (SVM) algorithm within their white paper.[46] In general, a machine learning-based approach is similar to a deep learning-based approach, requiring large datasets with images and the corresponding grades. The main difference between machine learning-based approach and deep learning-based algorithms is that the features used for prediction will need to be identified and created by human subject matter experts in order for algorithm development.

Deep learning-based

In contrast, the deep learning-based approach represents a more advanced AI technology that uses neural networks to analyse images. These algorithms allow the system to learn from a vast quantity of data, identifying subtle patterns and features within mammographic images. These features do not need to be created and are learnt during the training process. This method has proven to be effective in improving the accuracy and reliability of computer vision algorithms with the technology being well utilised in other healthcare use cases.[47,48] Within breast density assessment, algorithms have been developed using deep learning techniques. Based on internal test results, deep learning-based algorithms have surpassed the performance of traditional physics-based algorithms [43,44]. However, deep learning-based algorithms for breast density assessment are a recent development and the increased performance has not been translated into real world evidence.

Figure 5: Schematic of algorithmic-based approaches to characterisation of breast density



Source: Chalfant and Hoyt, 2022[25]

Due to commercial sensitivity, it is difficult to determine how each vendor has developed their current product. While vendors do share information about the initial algorithm development, details on subsequent ongoing development are often limited.[45] It is likely that vendors employ a variety of methods within their tools. These methods might include integrating multiple algorithms to pool results for more accurate outcomes or using different algorithms as quality control mechanisms to cross-verify and enhance the reliability of the final output.

The output produced by these AI tools is typically the volumetric breast density value, a numerical value that ranges from 0 to 100, where a score of 100 indicates extremely high

breast density. Each vendor would choose specific thresholds to represent the different BI-RADS classification and report the results as either the raw numeric value or classified into groupings. Additional metrics of total breast volume and fibroglandular volume is also presented to the end user.[46,49] Providing both volumetric breast density and absolute dense volume is important to ensure that breast size and area of dense volume can be considered, as is allowed for with the BI-RADS classification system. Studies have shown that absolute measures of dense tissue area or volume have greater predictive power of breast cancer risk than percentage or mammographic visual categorisation, though all measures are associated with increased risk of breast cancer.[50]

In terms of technical integration, the AI systems are designed to analyse raw Digital Imaging and Communications in Medicine (DICOM) images. DICOM is the global standard for storing and transmitting medical imaging information and related data. Once the AI has processed these images, the results are transferred into the Picture Archiving and Communication System (PACS). PACS is a medical imaging technology which provides storage and convenient access to each patient's images from multiple modalities. Within the PACS, these AI-generated results can be stored in two formats:

1. Standalone Structured Report: is a detailed report that outlines the findings of the AI analysis in a structured format. It includes the breast density score along with other relevant diagnostic information derived from the AI's interpretation of the mammogram. This format allows radiologists and other medical staff to quickly understand the AI's assessments in a comprehensive, organised manner.
2. Secondary Capture Image: Alternatively, the information might be saved as a Secondary Capture Image, which is a snapshot or image that contains the result. This is particularly useful for visual reference and comparison, providing a direct, illustrative representation of the findings that can be reviewed alongside the original mammograms.

5 Breast Density as a Risk Factor for Breast Cancer

5.1 Effects of Breast Density on Risk of Breast Cancer and Sensitivity of Mammography

Breast density has been shown to be an independent risk factor for the development of breast cancer and high breast density can obscure potential lesions on mammograms, thereby reducing the diagnostic sensitivity of imaging tests.[25]

The radiographic appearance of the breast varies among women because of differences in tissue composition.[51] Extensive mammographic density can make breast cancer more difficult to detect as tumours can be obscured by the appearance of normal dense tissue.[52] The sensitivity of mammography to detect cancer is inversely proportional to the degree of breast density, with up to 50% of cancers missed in mammograms on women with extremely dense breasts.[53,54]

Cancers detected in women with dense breasts have been shown to be larger, more aggressive[55] and are more frequently advanced with vascular or lymphatic invasion and spread to lymph node s.[56] Interval cancers appear to occur more frequently in women with dense breast tissue, with different risk estimates reported.[52,54] Contemporary evidence suggests extreme breast density carries around a two-fold increase in risk of interval cancers compared with women with lower density breasts.[57] A recent large British study reported twice the overall rate of interval cancers in women with the highest 10% breast density (Volpara measure) compared to the overall rate.[54] Mortality reduction from participation in the Dutch breast cancer screening programme was shown to be lower in women with dense breasts (>75% density)[58]. A Swedish study where 13% of women were classified as having dense breasts also demonstrated increased breast cancer mortality compared to other densities (after adjusting for other risk factors including stage), and this was considered mainly due to higher incidence of disease and partly poorer survival.[59] There is no consistent evidence currently that women with dense breasts once diagnosed have worse outcomes for equivalent subtypes compared with women with non-dense breasts.[60,61]

The exact mechanism responsible for development of cancer in dense breasts is unclear, however, there is substantial evidence to demonstrate the increased risk is independent and not due to missed identification alone, although the degree of independence is debated.[21] There is a consistent association over time of increased risk of breast cancer in women with high breast density. Studies of mammograms taken years before a breast cancer diagnosis show an increased association with cancer development long before it would be visible by mammogram.[52,62,63] Dense breasts have a greater proportion of stromal and epithelial tissue, which is where breast cancers arise, therefore, it is surmised that with a greater amount of this tissue comes a greater chance of cancer.[64] A linear trend of increased risk has been demonstrated when density is measured quantitatively.[54,65] Breast density may be considered as a continuum, with levels of breast cancer risk that can be variously categorised and thresholds debated.

Baseline density and changes over time have also been shown to be independently associated with the risk of breast cancer development. Women whose mammographic density is maintained or increases over time have been shown to have a higher risk of breast cancer than those for whom it decreases regardless of menopausal status. [66,67] The bodies hormonal milieu can modulate breast density and breast cancer risk, which has been demonstrated by a reduction in breast density and subsequent breast cancer risk

when taking the oestrogen blocker tamoxifen.[68–70] The use of post-menopausal hormone therapy, in particular, oestrogen plus progestin, has been shown to be associated with higher breast cancer risk among women with high breast density compared to post-menopausal women with high breast density that do not take hormone therapy. However, the relationship between hormone therapy and breast cancer risk appears to be additive and not fully mediated by a change in breast density. Women with low breast density have a lower risk of breast cancer, regardless of age, menopausal status and hormone therapy use.[71]

Obesity is another risk factor for breast cancer development. Obesity is consistently associated with an increased risk of breast cancer in post-menopausal women, however, the relationship in premenopausal women is not as clear with studies reporting both negative and positive associations.[72] Breast density and BMI are inversely correlated and appear to act as confounders to each other. [73]

There are also numerous studies showing associations between breast density and various subtypes of breast cancer, particularly for oestrogen receptor (ER)-positive disease. These relationships are important for the consideration of biological mechanisms responsible for tumour development and could be used to further develop risk prediction models and influence screening strategies.[74]

The magnitude of risk attributed to dense breast tissue varies from 2-6 fold across studies, which may be due to different ways of measuring and comparing density. The comparison group is important and risk will vary depending on this. For example, a meta-analysis of 42 studies using different density grading methods and comparing extreme densities found a 4-6 fold higher risk in women with >75% density compared with women with <5% density.[65] The best estimates are likely to be those comparing between a clinically defined high-risk group and all women or all women excluding the high-risk group. A recent meta-analysis of studies using the Breast Imaging Reporting and Data System (BI-RADS) density scale concluded that women with high breast density (density D) have a two-fold risk of breast cancer relative to density B, scattered fibroglandular tissue. [57] A two-fold increased cancer risk with high breast density compared to average density was also supported by an analysis of six American studies that all used the same density calculations[75].

As a comparison to selected other known risk factors for breast cancer (summarised below), presence of high penetrance genetic mutations, for example BRCA1/2, afford a greater than 5 fold increase in risk, whereas, moderate-penetrance mutations are associated with a relative risk of between 1.5 and 5. [76]

Table 1: Selected Known Risk Factors for Breast Cancer

Risk Factor		Relative Risk
Gender	Female vs Male	100.8[10]
Age	Older age (40-64 years vs 15-39 years)	9.4[10]
Genetic germline mutation carriers	High penetrance (BRCA1/2, TP53, STK11, CD1, PTEN)	≥5 and ≤12[76–78]
	Moderate penetrance (ATM, CHECK2, PALB2, BRIP1, RAD51, C/D)	≥1.5 and ≤5[76,78]
	Low penetrance (CASP8, FGFR2, H19, MAP3K1, LSP1, TNRC9)	≥1.01 and ≤1.5[76]
Familial related	One or more breast cancer affected first-degree relatives vs. none	1.70[79]
	Age of breast cancer affected first-degree relatives (younger than 50 years)	1.3–4[79,80]
Personal history	Systemic therapy for prior breast cancer and breast carcinoma in situ (BCIS)	>5[81,82]
	Benign breast lesions	1.17-3.93[83,84]
	Prior irradiation exposure	2.7-20[85,86]
Breast density	High mammographic breast density	2.0-5.0[65,87]
Hormonal related	Recent and long-term hormone replacement therapy	1.17–2.30[88]
	Oral contraception (less than one year vs. more than 10 years)	1.09–1.38[89]
Parity related	Age of first childbirth (over 35 years vs. before 21 years)	1.3–2.2[90]
Lifestyle related	Alcohol consumption (intake-dependent) vs. none	1.32–1.46[91]
	Physical activity (low vs. high level of activity)	1.12–1.23[92,93]
	Obesity (BMI > 30 kg/m2 vs. BMI <23 kg/m2) Pre-menopausal Post-menopausal	 0.54–0.98[94] 1.12–1.29[94]

Adapted from Tsarouchi et al. 2023[10]

6 Risk Assessment Tools

Risk assessment is central to a population level approach to cancer screening to ensure that the benefits afforded by screening outweigh the harms to those participating. Participants with greater risk are more likely to benefit, with the most basic level of risk stratification being age and sometimes gender.[95] Risk tools can produce risk estimates for individuals and be used to assign individuals to risk groups. The size of each risk group is an important consideration to enable planning of resources for risk-based screening protocols, and to help ensure relatively stable and accurate risk assessment and advice over time.[96] Numerous breast cancer risk models have been developed for different purposes. These mainly incorporate classical risk factors such as clinical, demographic or pharmacological exposures but may also include family history, genetic risk markers or polygenic risk scores and imaging related parameters to varying degrees.[97] The heterogeneity in model inputs, development and improvements to versions make direct comparisons complex. There is no single benchmark or performance metric that identifies a model as suitable for guiding personalised screening as this depends on the purpose of the tool. Models need to be robustly assessed in terms of discrimination, calibration and potential clinical utility in the target population.[98]

A 2023 review of studies comparing 11 breast cancer risk assessment tools found that no tool was consistently well-calibrated across multiple studies. Most tools were capable of identifying groups with higher rates of observed cancers across different settings but not lower risk groups. Tools that were recalibrated to the risk profiles of the population in which they were applied demonstrated an improvement in fit.[99] The most commonly assessed tool, the Breast Cancer Risk Assessment Tool (BCRAT or Gail Model) was developed by the National Cancer Institute in the USA. It uses personal medical, reproductive and family history to estimate absolute breast cancer risk over the next 5 years (up to age 90). Currently, three models, IBIS (Tyrer-Cuzick), BOADICEA (Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm) and BCSC (Breast Cancer Surveillance Consortium) are known to include breast density measurement in the calculation of risk. [100] AI algorithms that were developed to improve accuracy of breast cancer detection on mammography have also been shown to have comparable or better risk prediction than standard tools.[101] The Mirai model is an AI deep learning-based approach that uses full mammographic images in addition to traditional risk factors to predict 5 year breast cancer risk. This model was shown in retrospective studies to have improved risk prediction compared to the IBIS model across a number of international datasets.[102,103] The combination of a mammographic AI algorithm for cancer detection (Transpara) and clinical risk factors, including breast density measurement has been shown in one study to improve long-term risk prediction (including overall invasive cancers, screen-detected, advanced, and nonadvanced cancers).[104] However, the addition of clinical factors to AI image prediction does not always result in significantly improved risk prediction.[101] A number of clinical trials (see Research on Risk Stratification

Approaches) are allocating women to risk-based screening protocols based on their predicted risk of breast cancer estimated with risk assessment tools, including those that incorporate breast density.

How breast cancer risk thresholds are set is complex, varies from country to country and remains inconsistent, with high-risk definitions ranging from 20-30% lifetime risk.[105] The thresholds set by different countries have been developed based on evidence and local context. Risk can be expressed as a lifetime risk from birth, remaining lifetime risk and risk for a fixed horizon e.g 5 years. As breast cancer incidence and mortality change with age and over time so too do risk estimates. Studies suggest that breast cancer risk stratification models will likely be more accurate when based on predicted short term risk compared with risks based on predicted lifetime and remaining lifetime, particularly for younger women.[106,107]

NICE clinical guidelines indicate that a 30% lifetime risk is equivalent to an 8% chance of developing breast cancer between the ages of 40 and 50.[108] The "Standards of Service Provision for Breast Cancer Patients in New Zealand 2013" (the Standards NZ) provide the Cancer Australia risk thresholds as good practice points. Women are considered high-risk when their calculated lifetime risk is 25% or higher and recommend annual MRI.[109] The Royal Australian College of General Practitioners recommends supplemental ultrasound or MRI for asymptomatic women with a risk of breast cancer three times above the population average, and the Australian government guidelines recommend annual MRI and mammography before age 50 for women with 30% or greater lifetime risk of breast cancer, and annual mammography for those with a 17 to 30% lifetime risk. [110,111]

Table 2: The Standards NZ Breast Cancer Risk Categories

Risk	High	Moderate	Average
Lifetime risk (up to 75 years)	>25% 1 in 2 to 1 in 4 women	12-25% 1 in 4 to 1 in 8 women	9-12% 1 in 8 to 1 in 11 women
Percent of female population	less than 1%	4%	95%

Based on Cancer Australia risk categories[109]

The Australian website, eviQ, is a free web-based resource of evidence-based protocols and information intended to be used by health professionals at the point of cancer care delivery. It has been developed for the Australian context but has been considered appropriate for use in Aotearoa New Zealand. It has produced guidelines on surveillance for individuals who are BRCA1 or BRCA2 carriers, or otherwise considered at high-risk.

Individual risk assessment using CanRisk or equivalent validated tools is recommended, which can be accessed through the eviQ website.[112]

CanRisk is a validated and internationally endorsed tool developed through Cambridge University to calculate cancer risks for individuals, including mutation carrier probabilities. It is designed to provide formats that assist healthcare professionals to communicate results to individuals. It uses the clinically validated BOADICEA model to calculate breast (and ovarian) cancer risks using individual level information including personal risk factors, family history, genetic testing, and mammographic density where known. BOADICEA was developed as a comprehensive risk stratification tool for the general population and those considered at higher risk of breast or ovarian cancer.[113]

In the late 1980s an Aotearoa New Zealand specific breast cancer risk calculator tool was developed.[114,115] The relative risks for selected predictors were combined with baseline breast cancer incidence rates and non-breast cancer mortality rates to calculate individual probabilities of developing breast cancer within 5 years. The model predicts risk in women aged 25-54 and is designed for use in unscreened asymptomatic women. The lifetime risk of female breast cancer in Aotearoa New Zealand is 1 in 9 and the calculated individual risk varies based on factors including age, ethnicity, age at menarche, age at menopause, parity, oral contraceptive use, family history of breast cancer, and history of thyroid or breast disease. Breast density is not incorporated into this model and the model is not recommended for women with a strong family history of breast or ovarian cancer or a BRCA gene mutation.[116] Whether this calculator is used clinically in Aotearoa New Zealand is unknown. The Standards NZ recommend the use of iPrevent (a web based decision support tool that estimates breast cancer risk utilising the IBIS and BOADICEA models), BCRAT/The Gail Model or the IBIS tool for calculation of breast cancer risk.[109]

7 Supplemental Screening

Supplemental imaging in breast screening is imaging used in addition to standard screening pathways. It is a term most often used in the context of breast density where it is used to improve sensitivity for breast cancers. Supplemental imaging is distinct from technical recalls when a radiologist is not satisfied with the quality of mammograms, or as additional imaging undertaken as part of any recall to assessment, determined following reading of standard screening mammograms – these would be considered part of the standard screening pathway. A number of potential supplementary screening strategies (alternate modalities and alternate intervals) have been considered internationally. The following table outlines a range of potential supplemental screening modalities:

Table 3: supplemental screening modalities

Modality	Description	Sensitivity	Comment
Additional Mammogram e.g annual	Creates a 2D breast image using multiple X-rays. Uses ionising radiation and breast compression.[117]	25-59% mainly in high-risk populations[118]	Not generally recommended due to low sensitivity.[21] Repeated exposure to radiation not recommended for younger women due to increased cancer risk associated with radiation.[119]
Ultrasound (US)	Uses soundwaves to image tissue, no radiation or contrast required.[4]	80%-83% mainly in high-risk populations[42,120]	Improved cancer detection compared to standard mammography.[121] Suggested in addition to mammography[122,123] or alternate annually.[124]
Contrast-Enhanced Mammography (CEM)	An X-ray subtraction technique, requires iodinated intravenous contrast and involves radiation exposure.[3] Not widely available in New Zealand.	91%-96% in patients with suspicious breast lesions on prior imaging[125–127]	Similar sensitivity to MRI in women with dense breasts.[128] Suggested supplemental screen for high-risk women (lifetime risk ≥ 25%).[129]
Digital Breast Tomosynthesis (DBT)	Uses multiple X-ray images to create a 3D breast image.[4] Limited availability in Aotearoa New Zealand.	88% (average risk of cancer) [130,131]	Modestly improved cancer detection compared to standard mammography. Suggested alternative for routine mammographic screening but no mortality results available yet. [132]

Modality	Description	Sensitivity	Comment
Contrast-enhanced Magnetic Resonance Imaging (MRI) or abbreviated MRI	Uses magnetic and radiofrequency fields to produce 3D images. Requires intravenous contrast.[7] Abbreviated MRI protocols are shorter in duration[133] and is available in a number of private providers in New Zealand.	81-100% mainly in high-risk populations[118,134]	Most sensitive imaging modality, preferably identifies more aggressive/invasive cancer.[135] Used in high-risk groups as both screening and supplemental screening tool.[136]

7.1 International Supplemental Screening Practice

Current guidelines for supplemental breast screening are limited to women deemed to be at high-risk of developing breast cancer. Therefore, the lack of consensus and lack of use of formal risk assessment protocols can be a barrier to implementing supplemental screening, with appropriate and consistent application required to identify those who may be recommended for supplemental screening.

Guidelines on the imaging type used for supplemental screening vary, mainly due to the availability of resources. Since discovery of the BRCA1/2 gene mutations for breast cancer susceptibility in the mid-1990s, MRI has been used as a screening tool for women with high breast cancer risk. MRI was first recommended for women with a lifetime breast cancer risk of ≥20% by the American Cancer Society in 2007[137]. Breast MRI does not use ionising radiation but does require intravenous injection of contrast medium. Studies have demonstrated superiority of MRI over mammography for cancer detection in women with higher risk[136,138]. A recent meta-analysis of cancer detection rates for high-risk women in diagnostic studies using MRI, mammography or both demonstrated that a combination was best for identification of cancers.[139]

However, MRI is not always appropriate due to contraindications (e.g. metalware, pacemakers), claustrophobia, availability and cost.[140–142] Abbreviated MRI is a more efficient, tailored protocol specifically aimed to detect the presence or absence of cancer, that is as effective diagnostically as standard MRI, whilst reducing cost and improving accessibility.[143]

Standard mammography, that creates 2D images from multiple x-rays, is not generally recommended as a supplemental screening method due to low sensitivity in high-risk women[118] and the harmful risk of radiation exposure for younger women.[119] However, a

Canadian retrospective study comparing the interval cancer rates of annual vs biennial screening for women with dense breasts demonstrated a reduction in interval cancers for those screened annually.[144] Thus, suggesting that women with dense breasts may benefit from an annual screening programme.

Contrast-enhanced digital mammography (CEM) is a simpler, lower cost alternative to MRI that utilises intravenous contrast injection in combination with X-ray image subtraction. It has been shown to be more sensitive than mammography and ultrasound for detecting breast cancer, including in a screening population [145–147] and has similar sensitivity to MRI with respect to cancer detection and tumour size estimation.[148] CEM has been reported to improve cancer diagnosis in dense breasts compared with mammography.[128] This could be a good alternative for those that cannot undergo MRI, however, radiation exposure may exclude use for younger women and at present it is not widely available in Aotearoa New Zealand.

Breast ultrasonography (US) uses sound waves to image tissue, it is widely available (although with capacity issues within the public healthcare system in Aotearoa New Zealand) with no radiation or intravenous contrast required. Initial clinical studies showed no value in the use of ultrasound to detect cancers in asymptomatic women with a negative mammogram. However, by the mid-1990s improvements in technology resulted in the detection of cancers missed on mammograms.[149] It was subsequently demonstrated to identify small sized, node negative tumours not visible on mammography[149–151] and increase cancer detection rates in women with dense breasts,[122] however, at a rate much lower than MRI but with similar specificity (as described in Table 4 Outcomes from Supplemental Screening after standard 2D Mammography in women with dense breasts (or all densities for MRI)).

Digital Breast Tomosynthesis (DBT) or 3D mammography uses multiple X-ray images to create a 3D breast image. A reduction in the superimposition of imaging fields allows for visualisation of abnormalities that may be obscured by overlapping tissue. Increased visibility allows for better identification of tissue architecture, minimising overdiagnosis and reducing recall rates for assessment.[152–154] Support for the use of DBT in routine screening has been demonstrated in a number of studies showing improved and earlier cancer detection and improved specificity. [33,155,156] DBT was initially utilised in addition to digital mammography and improvements in cancer detection and specificity were observed.[152,157,158] However, it has been suggested to be better utilised for routine screening rather than for supplemental or high-risk screening. A study investigating the effectiveness of DBT screening showed benefit for women with heterogeneously dense breasts but none for women with extremely dense breasts.[154] DBT is available in a number of private providers in New Zealand, with limited availability outside of this.

7.2 Supplemental Screening Modality Outcomes

Any modality of breast screening has benefits and harms to the patient. In the context of supplemental screening three metrics have been described in the literature to quantify and compare modalities – the incremental cancer detection rate, recall rate and interval cancer rate.

The incremental cancer detection rate is the number of additional cancers detected at screening with a particular modality relative to another. This is often stated as a percentage of screens or as a rate per 1000 screens.[5]

The recall rate is the number of women recalled for further assessment as a proportion of all women who were screened. A recall may be a consequence of the screening mammogram, for (i) a repeat mammogram because of technical inadequacy of the screening mammogram (technical recall) or (ii) clarification of a perceived abnormality detected at screening, by performance of an additional procedure (recall for further assessment).[5] The additional false positive recall rate is the percentage of women recalled who were found to not have cancer.

An interval cancer is a primary breast cancer diagnosed in a woman who had a result in a screening test, with or without further assessment, that was negative for malignancy, either (i) before the next invitation to screening was due or (ii) within a period equal to a screening interval for a woman who has reached the upper age limit for screening. This may be expressed as a rate, which is the number of interval cancers diagnosed within a defined period since the last negative result in a screening examination, per 1000 women with negative results.[5]

A comparison of supplemental screening outcomes with regards to cancer detection predominantly in women with dense breasts (all densities for MRI) was summarised by Berg et al 2023[100] (see Table 4 below). With regards to cancer detection MRI has the highest rate of incremental detection at between 6-20 per 1000 screens, with CEM the next best improvement at 7-13 per 1000 screens. Supplemental screening with ultrasound and DBT provides a modest improvement in cancer detection. All methods of screening are associated with false positive recalls, which decrease with subsequent rounds. In women with dense breasts ultrasound and MRI screening results in an average recall rate of 8-11% with first screens, which decreases to between 2% and 5% with subsequent screens.[159,160] Overall, CEM has an average recall rate of 6.5%.

Table 4: Outcomes from Supplemental Screening after standard 2D Mammography in women with dense breasts (or all densities for MRI)

Method	Incremental Cancer Detection Rate per 1000	False Positive Recall Rate	Interval Cancers Reduced
US* (first round)	2–3[161]	8%–12%[123,161,162]	Yes
US (subsequent rounds)	1–3[123,162,163]	2%–5%[123,162,163]	Yes
Contrast-enhanced mammography (CEM)	7–13[146,164–166]	6.5%[146,164–166]	Unknown
DBT	1.2-1.4 [152,154]	Unknown	Unknown
MRI or abbreviated MRI (first round)	10–20[123,159,167–169]	9%[123,159,167–169]	Yes
MRI (subsequent rounds)	6–7[169,170]	2%[169,170]	Yes

*US – ultrasound

Adapted from Berg et al. 2023[100]

7.3 Breast screening benefits and the potential additional benefit of Breast Density reporting

Population-based mammography screening programmes have been shown to decrease breast cancer mortality, although estimates vary in magnitude and across age groups. [171–173] However, identifying mortality benefit from mammography can be challenging[174] and there are known issues in breast screening programmes with estimation of overdiagnosis, false positive results and false negative results or interval cancers[171,175]. Screening programmes can also reduce morbidity with early diagnosis enabling less extensive surgical procedures (e.g. breast conserving surgery), and avoidance of adjuvant therapy, and more recently lower intensity radiotherapy.[176–179] The potential benefits and risks of reporting breast density are dependent firstly on the standard screening programme plus the addition of density measurement and any subsequent screening modality. These issues are further discussed below.

Benefits

Mortality

The benefits of breast density reporting and resultant supplemental screening are currently difficult to quantify, particularly given that overall breast cancer survival is high compared to other cancer types[180]. It should be noted that overall breast cancer mortality in New Zealand is 16% higher than Australia.[181] Due to the time required to evaluate mortality data, no randomised controlled trials have yet demonstrated decreased mortality due to supplemental screening for any high-risk populations.[136]

A case control study published in 2017, from within the Nijmegen (Dutch) screening programme (1975- 2008) looked at screening outcomes, including cancer mortality in women aged 50-74 years with dense breasts compared to women with non-dense breasts. These women received biennial, screen-film 2D mammography, with density measured using a 4 scale category based on the Wolfe breast density pattern (similar to BI-RADS). Analyses of mortality odds ratios were based on 333 breast cancer deaths occurring between 1977 and 2008, demonstrating an overall 33% lower risk of breast cancer death for women who participated in screening in the 4 years prior to diagnosis compared with women who did not participate. However, the estimated mortality reduction from participating in the screening programme was less for women with dense breasts compared to those with non-dense breasts (13% for dense compared to 41% for non-dense breasts).[58] Furthermore, results from the Kopparberg randomised controlled trial in Sweden published in 2010 also confirmed that women with dense breasts have a higher incidence of cancer, increased breast cancer related mortality but no difference in survival once diagnosed. This trial measured baseline breast density with the Tabar classification from screen-film 2D mammography. It prospectively followed 15,658 women aged 45-59 randomised to invitation to screening or no invitation between 1977 and 1981. Enrolled women who were offered screening every 2-3 years (depending on age) were prospectively followed up until 2004, with an average follow-up of 25 years [59] An American study of over 9,000 women with primary invasive breast cancer, with a mean follow-up of 5 years, concluded that high breast density was not associated with risk of death from breast cancer or death from any cause after accounting for other patient and tumour characteristics.[61] Therefore, for women with dense breasts there is an increased incidence of cancer, decreased mammographic sensitivity and in some studies, increased mortality from these factors. However, a difference in survival after diagnosis has not been consistently shown. However, the findings from these studies suggest that providing a supplemental screening approach to women with dense breasts could result in improved cancer detection and improved outcomes for these women.

Morbidity

In the absence of survival comparisons for women with dense breasts treated with or without supplemental screening the next best outcome measures are cancer detection

rates, stage at diagnosis and interval cancer rates. Increased cancer detection may lead to earlier diagnosis of breast cancer with the possibility of treatment at an earlier stage, thus potentially decreasing morbidity and mortality.

Numerous studies, including randomised control trials comparing mammography alone with mammography combined with a supplemental screening test in high-risk women have illustrated statistically significant increases in cancer detection rates. [123,150,182–184] and earlier detection of cancer, reducing incidence of late stage cancers, which could decrease the need for adjuvant therapy and reduce mortality.[185]

A 2018 meta-analysis of twenty-nine studies published after the year 2000 and including over 100,000 screen results concluded that women with dense breasts who underwent supplemental ultrasound screening reported an average 40% increase in the detection of cancers compared to mammography alone. This equates to an additional 3.8 screen-detected cancers per 1000 mammography-negative women. There was heterogeneity in the studies included with respect to screening types and regimes, study populations, age range and importantly density classification. The inclusion of women with lesser breast density (scattered) slightly diluted the benefit of additional cancer detection by US. Addition of ultrasound was of slightly more benefit after film screen mammography compared to digital mammography.[186]

The Japanese J-START randomised controlled trial primary analysis published in 2016 reported on over 72,000 women aged 40-49 years randomised to receive either mammography and supplemental ultrasound, or mammography alone. With the addition of ultrasound the cancer detection rate increased from 0.32% to 0.5%, detection of earlier stage cancers (0 and 1) increased from 52% to 71% and there was a decrease in the interval cancer rate from 0.1% to 0.05%.[124] A subsequent secondary analysis of 19,000 records with corresponding breast density measures published in 2021, confirmed increased sensitivity and improved detection of early-stage and invasive cancers in women with dense breasts who receive supplemental ultrasound.[187] The 2019 DENSE clinical trial investigated the incidence of interval cancer in over 40,000 women with dense breasts, aged 50-75 years old, whom were participating in the Dutch population-based, biennial, digital mammography screening programme. Approximately 4,700 women with extremely dense breasts and a negative mammogram result underwent supplemental MRI screening. A reduction in interval cancers from 5.0 per 1000 to 2.5 per 1000 screenings was observed with the first round of MRI screening compared to the mammography only group.[159]

Breast cancers detected by screening in general have more favourable characteristics, they are smaller, of lower grade, are less likely to metastasise, and require less extensive treatments, although the debate about the magnitude of overdiagnosis in this context is noted.[176–178] Women who participate in breast screening programmes have been shown to have lower rates of mastectomy, lower rates of radiotherapy post mastectomy, fewer

axillary dissections and fewer recommendations for chemotherapy compared to women who do not participate in breast screening programmes.[179] This has implications for short and long term quality of life. Breast cancer survivors have reported significant long term adverse effects that vary depending on the type of treatment received.[188] Breast conservation is associated with a better quality of life compared to mastectomy[189]. Sentinel node biopsies are preferable over axillary dissections due to less perceived pain, stiffness and lymphedema[190,191], whilst chemotherapy and radiotherapy have well recognised acute and long term side effects.[192–195] Therefore, early detection and tumour characterisation at diagnosis should help to tailor treatments effectively and minimise harms.

In addition to the morbidity benefits of early cancer detection, treatment costs for early stage breast cancers are reduced compared to late stage breast cancers. A 2024 systemic review including 53 studies estimating the economic burden of breast cancer in the USA, Canada, Australia and Western Europe found that despite heterogeneity in study design and cost estimation, metastatic breast cancer was associated with higher costs than earlier-stage cancer.[196] An earlier systemic review from 2018 including 20 studies from 10 different countries concluded that cost data by stage was limited and hard to compare, however, in general treatment costs by stage at diagnosis increased with advancement of stage.[197] A 5-year follow-up study, published in 2022, of public healthcare costs associated with breast cancer treatment in Aotearoa New Zealand confirmed that treating patients with early stage breast cancer was less costly than treating those with metastatic disease.[198]

7.4 Breast screening harms and the potential additional harms of Breast Density reporting

In Aotearoa New Zealand the national breast screening programme is estimated to reduce breast cancer mortality by 30% in regularly screened women (screened ≥3 times and mean screening interval ≤30 months).[13] There are inequities in access to the programme by ethnicity with only 63% of eligible wāhine Māori screened in the last two years (as at January 2025) compared to 73% of Other (non-Māori, non-Pacific, non-Asian) women.[199] Wāhine Māori also have a higher prevalence of breast cancer, and an increased mortality rate relative to European women.[200–203] Given that wāhine Māori may have higher breast density[37], this is a potentially compounding risk factor to the access inequities which already exist for Wāhine Māori. Further to this, measuring breast density and provision of supplemental screening would come with a cost. Screening services in Aotearoa New Zealand share limited resources, often with symptomatic breast care services. Therefore, any extra demands placed on screening services could have unintended consequences for access to diagnostic and screening tests for symptomatic patients and current screening participants.[204]

Given that 50% of the population potentially have dense breasts (10% extremely and 40% heterogeneously), supplemental screening could possibly impact many women. As the prevalence of density, including any ethnic variability in Aotearoa New Zealand is unclear, this has major implications for informing recommendations on breast density reporting in the Aotearoa New Zealand context. An American study calculating a 5 year breast cancer risk using the Breast Cancer Surveillance Consortium (BCSC) model demonstrated that not all women with dense breasts have a high-risk of interval cancer. Therefore in the absence of consideration of risk factors other than dense breasts, half of women could undergo supplemental screening unnecessarily. Conversely, using the combination of breast cancer risk and breast density improves identification of women at high-risk compared with age and breast density alone.[205] The addition of breast density measures to standard risk prediction tools also improves identification of high-risk women.[206] Therefore a combination of breast density and other risk factors may be required to target women with dense breasts who are at the greatest risk of developing cancer.

The main harm of breast screening is overdiagnosis, which is characterised by the detection of cancers that may have never advanced to hazardous disease.[207] Unnecessary treatment is harmful for the patient and reduces the cost effectiveness of screening, however, there is currently no way to avoid some level of overdiagnosis and it is difficult to estimate the magnitude of the problem. Overdiagnosis can be estimated, although rates vary depending on the methodology used.[208] Randomised clinical trial estimates range from 10-30% overdiagnosis of breast cancer.[209–212] A study of breast cancer incidence rate trends in Aotearoa New Zealand following the 2004 age range extension to the BSA programme concluded that there was no evidence of screening related overdiagnosis.[213] There needs to be a balance between increased sensitivity to identify cancerous tissue and decreased specificity of the imaging modality.

As discussed earlier, false positive findings that lead to a recall for assessment are an expected outcome of mammographic screening. Most recalls result in additional imaging (10% of all screens[214]), with approximately 6% of women regularly screened (over a 10 year period) receiving a biopsy that does not reveal cancer[215]. The 2019 DENSE clinical trial demonstrating reduced interval cancers with supplemental MRI for women with dense breasts had an overall recall rate of 9.5% and a biopsy rate of 6.3%. The false positive rate[1] was 8%, and 74% of women who underwent biopsy on the basis of MRI did not have cancer. [159] False positive rates for BreastScreen Aotearoa were 7.3% for initial and 2.6% for subsequent screens of all women screened aged 50-69 years between July 2020 and June 2022.[17]

The anxiety associated with additional testing is generally deemed acceptable by women surveyed in return for the benefit of early diagnosis.[216] False negatives occur when a

[1]In this study, the false positive rate was defined as “the percentage of women who had a positive result on screening MRI but who were later found not to have breast cancer”.[159]

mammogram is reported as normal, but a cancer is present and interval cancers are cancers that are found in the interval between a negative screen and the time a next screen would have occurred. While these can be cancers that develop between screening rounds, they may be due to screening modality limitations, technical or clinical interpretation errors and represent underdiagnosis. [10]

If supplemental screening was not funded in Aotearoa New Zealand, women with dense breasts would have to cover the additional cost of supplemental screening which could create stress, fear and anxiety if women cannot afford this and could introduce further inequities in screening access and outcomes. Supplemental screening tests are generally only covered under health insurance for women who, based on risk calculators, have a high lifetime cancer risk (25% in Aotearoa New Zealand), a threshold that most women with dense breasts will not meet in the absence of other risk factors. Women in Aotearoa New Zealand aged 40-50 years considered 'moderate' risk (12-25% lifetime risk) should be offered annual mammography (see Appendices: Management of BRCA in Aotearoa New Zealand). This is the scenario that many women with dense breasts would fall within.[109,217]

Comparative modelling of supplemental ultrasound screening for women with dense breasts suggested that the addition of ultrasound screening after a negative mammogram would substantially increase costs while producing relatively small benefits in breast cancer deaths averted and QALYs gained. [218]

8 Breast density reporting

8.1 Internationally

Breast density reporting within screening programmes is becoming more widespread. In December 2023 the Royal Australian and New Zealand College of Radiologists (RANZCR) recommended 'mandating the reporting of breast density in both screening and diagnostic settings in Australia and New Zealand'.[219] BreastScreen Australia does not require providers to report breast density although it is voluntarily reported by New South Wales, Western and South Australia screening programmes. A National Policy and Funding Review of BreastScreen Australia is in progress to develop recommendations for evidence-based best practice in breast cancer screening[220] with a trial being run in Queensland to investigate various psychosocial outcomes and health service use related to reporting breast density.[221]

The National Health Service (NHS) Breast Screening Programme in England does not currently include assessment or reporting of breast density on screening mammograms.[222] Though the recently published study discussed earlier of a consecutive English screening

cohort has concluded that mammographic sensitivity and specificity decreases whilst interval cancers increase with increasing breast density and consideration should be given to offer supplemental imaging to women with extremely dense breasts.[54]

In Canada, 12 of 13 provinces/territories have independent breast cancer screening programmes that vary in participation criteria, however, breast density is reported in 11 of these. [223] In 2022, the European Society of Breast Imaging (EUOSBI) recommended that women should be appropriately informed about their breast density, and on the diagnostic and prognostic implications of having dense breasts.[224] An analysis of national breast screening guidelines in Europe found that as of 25 April 2023 the following countries reported breast density: Austria, Bulgaria, Croatia, Cyprus (for BI-RADS categories C and D), France, Greece, Hungary, Serbia and Switzerland.

From 10 September 2024 in the United States of America (USA) all mammogram result letters to women must report whether the breasts are “dense” or “not dense” and the report to providers must report the BI-RADS density category. [100,225]

Breast density reporting internationally needs to be considered in the context of different health care systems. Comparisons between these systems can be complex. Most of the countries discussed above have universal or near-universal health coverage. However, health system funding is varied. Similar to Aotearoa New Zealand, countries such as England, Canada, Italy, and Norway have largely publicly funded and operated health systems. Some, including Australia, France, Croatia, and Germany have mandatory publicly funded insurance whereas others, such as the Netherlands, have a mix of private (non-profit and profit) and public insurance. The United States has a voluntary private insurance system more recently supplemented by public insurance programmes. With this funding, each country provides different levels of service provision. These system differences will influence breast density reporting practices.[226,227]

Table 5: Breast Density reporting status in International screening programmes

Country	Breast density reporting in the national screening programme	Comments
Australia	Partial	Reported in New South Wales, Western Australia and South Australia[24,228,229]
Canada	Yes	In all provinces with an organised screening programme[223]
United States of America*	Yes	Mandated from 10th September 2024[225]

Country	Breast density reporting in the national screening programme	Comments
United Kingdom and Ireland	None	
Europe: Austria, Bulgaria, Croatia, Cyprus, France, Greece, Hungary, Lithuania, Serbia, Switzerland	Yes	Known European countries that report density as at April 2023[222]
Europe: Germany, Iceland, Italy, The Netherlands, Norway	None	Known European countries that do not report density as at April 2023[222]

* does not have a national organised screening programme, considered opportunistic

8.2 Supplemental Screening Guidelines

Currently, there is no consensus guideline uniformly recommending supplementary screening based on dense breasts alone. However, women with dense breasts and other risk factors often have an estimated lifetime risk ≥20% and can meet high-risk screening criteria. Current recommendations from professional organisations and guideline development groups on supplemental screening for women with dense breasts are summarised below with further detail in the appendices.[230] The European Society of Breast Imaging (EUSOBI) recommends adding screening MRI every two to four years in women aged 50 to 70 years who have extremely dense breasts. The American College of Radiology (ACR) recommendation for women with dense breasts is annual mammography, annual MRI, and to consider CEM or ultrasound as an alternative to MRI (at 40 years or earlier if other risk factors present).[231] The German Gynaecological Oncology Working Group (AGO) recommend breast ultrasound for heterogeneously or extremely dense breasts and MRI if a screening mammogram is negative and breast

composition is extremely dense for women aged 50-75. The American based National Comprehensive Cancer Network (NCCN), The American Cancer Society (ACS), the ACR, and EUSOBI all recommend annual MRI when dense breast is present in combination with other risk factors that result in a lifetime risk of ≥20%.[100] The German Guideline Program in Oncology, The Brazilian College of Radiology and Diagnostic Imaging (CBR), Brazilian Breast Disease Society (SBM), The Brazilian Federation of Gynaecological and Obstetrical Associations (Febrasgo) and the China Anti-Cancer Association all recommend or advise considering supplemental screening with ultrasound.[230]

Some professional organisations and guideline development groups have concluded that there is insufficient or limited evidence to make a recommendation on supplemental screening for women with dense breasts. This includes The European Commission Initiative on Breast Cancer Guideline Development Group, The United Kingdom National Screening Committee, The Royal College of Radiologists (United Kingdom), The Japanese Breast Cancer Society, The American College of Obstetricians and Gynaecologists, the American Cancer Society, The United States Preventive Services Task Force and The American Academy of Family Physicians.[230] The Royal Australian and New Zealand College of Radiologists position statement updated in 2023 suggests that the EUSOBI screening statement is an aspirational goal and that breast density reporting should be mandated whilst a future risk-based model for breast cancer screening is developed. [219]

Table 6: Summary of breast density related screening guidelines/recommendations/position statements

Professional Organisation	Year	Measure Breast Density	Supplemental Screening	Recommendation and relevant comments
European Commission Initiative on Breast Cancer Guideline Development Group (GDG)[232]	2020		No	Tailored screening for mammographic breast density
European Society of Breast Imaging (EUSOBI)[224]	2022	Yes	Yes	SS with MRI* at least every 4 years, preferably every 2–3 years for women with extremely dense breasts aged 50–70. US in combination with DM* may be used
The German Guideline Program in Oncology	2021		Yes	SS with US, consider tomosynthesis

Professional Organisation	Year	Measure Breast Density	Supplemental Screening	Recommendation and relevant comments
(German Cancer Society, German Cancer Aid, Association of Scientific Medical Societies (AWMF))[233]				
The German Gynaecological Oncology Working Group (AGO)[234]	2020		Yes	Breast US* for heterogeneously dense, extremely dense mammograms. MRI if screening mammogram is negative and breast composition extremely dense 50–75 years old
The Royal College of Radiologists (United Kingdom)[235]	2019	High-risk	No	
The Royal Australian and New Zealand College of Radiologists[219]	2023	Yes	No	Aspirational goal to follow EUSOBI guidance
The Brazilian College of Radiology and Diagnostic Imaging (CBR), Brazilian Breast Disease Society (SBM), and Brazilian Federation of Gynecological and Obstetrical Associations (Febrasgo)[236]	2017		Yes	Complementary US should be considered
Alberta Breast Cancer Screening Clinical Practice Guideline[237]	2022		Yes	Annual mammography and consider annual breast ultrasound and consider annual clinical breast exam

Professional Organisation	Year	Measure Breast Density	Supplemental Screening	Recommendation and relevant comments
China Anti-Cancer Association[238]	2019		Yes	Breast US
The Japanese Breast Cancer Society[239]	2018	Yes	No	
American College of Radiology[240]	2023		Yes	DBT* screening usually appropriate Annual mammography and annual MRI Consider CEM or ultrasound as alternative to MRI (Age 40 or earlier if other risk factors)
American College of Obstetricians and Gynecologists[241]	2020	Yes	No	
American Cancer Society[137]	2007		No	
The National Comprehensive Cancer Network[242] (American)	2024		Yes	For individuals ≥40 years of age with heterogeneous or extremely dense breasts, consideration should be made for supplemental screening
The Society of Breast Imaging[243]	2010		Yes	US
The United States Preventive Services Task Force (USPTSF)[244]	2016		No	
The American Academy of Family Physicians[245]	2021		No	

*Abbreviations: SS = Supplemental screening, IV= Intravenous, DM = Digital Mammography, US = Ultrasound, DBT = Digital Breast Tomosynthesis, MRI = Magnetic Resonance Imaging, CEM= Contrast Enhanced Mammography

Source: Adapted from: O'Driscoll et al. 2023[230]

8.3 Ethical and legal considerations

The framework for ethics analysis of public health programmes proposed by Kass (2001) states that "public health interventions should reduce morbidity or mortality; data must substantiate that a program (or the series of programs of which a program is a part) will reduce morbidity or mortality; burdens of the program must be identified and minimized; the program must be implemented fairly and must, at times, minimize preexisting social injustices; and fair procedures must be used to determine which burdens are acceptable to a community".[246] Considering these factors with regards to notification of breast density within a breast screening programme raises a number of ethical perspectives, some of which have been mentioned in preceding sections, and some are discussed below.

There is uncertainty in the measurement and management of breast density. Mammographic visual assessment of breast density is subjective, though this could be partially addressed with the use of validated automated measurement. The appropriate clinical pathway is also unclear with survival data not yet available from clinical trials evaluating supplemental screening in women with dense breasts.[247] Enhanced and earlier cancer detection has been reported with the addition of supplemental screening, however, this can be associated with increased false positives. [124,159,186] This raises concern that any benefits gained from supplemental screening could result in harms to some from overdiagnosis. There would also be additional costs to the programme that would be dependent on the screening modality used and would need to be considered. This uncertainty makes it difficult to evaluate outcomes, fairness and acceptability for participants of the programme and to evaluate potential opportunity costs.

Known inequities already exist in breast cancer outcomes overall, particularly the symptomatic pathway[201,248], and also in access to the BreastScreen Aotearoa programme by ethnicity, deprivation level and place of residence.[199] It is likely that socio-economic deprivation, income levels, urban/rural residence, and comorbidities also influence interactions with the breast cancer screening programme in Aotearoa New Zealand.[249] Women with dense breasts are at a greater risk of developing cancer, have higher rates of interval cancers that are more advanced at the time of diagnosis and do not have the same mortality benefit from population-based mammographic breast screening as women with non-dense breasts. This all suggests that there is also inequality for women with dense breasts in the opportunity to benefit from early diagnosis of breast cancer associated with screening. If supplemental screening is not available to women with dense breasts through the public health system, it will not be accessible to many due to cost. There is already inequity in the current system, as breast density is measured and reported by most private providers of breast screening in Aotearoa New Zealand. These parameters of inequity are unfair, potentially compounding and are likely to further disadvantage some groups of women already facing inequities, for example, wāhine Māori

with dense breasts. The code of expectations for health entities' engagement with consumers and whānau, published by the Health Quality and Safety Commission and required by the Pae Ora Healthy Futures Act 2022 sets the expectations for health entities, including to promote equity and to engage with those with greater health needs, particularly Māori, Pacific peoples and disabled peoples.[250,251]

Providing adequate and effective breast density information supports women's autonomy to make informed decisions about their care.[247] There are two issues to consider, firstly, the act of providing information on personal breast density and secondly what to do once presented with that information. It has been established that breast density is associated with risk of cancer development and reduced detection on mammography, and that some modalities of imaging are more sensitive at detecting breast cancer in dense breasts. In Aotearoa New Zealand the Code of Health and Disability Services Consumers' Rights establishes the rights of patients, and the obligations and duties of healthcare providers. Right 6 specifically outlines the right to be fully informed, including (but not limited to) the results of tests and an explanation of the options available, an assessment of expected risks, side effects, benefits and cost options, with Right 7 detailing the right to make an informed choice and give informed consent.[252] Therefore, if breast density was measured but not disclosed to women this would be depriving women of their right to be fully informed and make an informed decision. The lack of guidance and consensus on how best to clinically manage women with dense breasts may be perceived as unhelpful, and concerning for women, however, it highlights the importance of providing clear information on the harms and benefits of participation. A well-considered and thorough consent process will help to alleviate the issue of uncertainty. What information and how best to provide it could be extrapolated from international evidence, however, ideally this needs to be explored in the Aotearoa New Zealand setting to allow Aotearoa New Zealand women to make the best decisions. Furthermore, to facilitate consent for a complex issue is time consuming and cognitively stressful for healthcare professionals already under significant pressures. Where this responsibility would sit needs to be considered within a health care system already affected by significant capacity issues including the current rollout of breast cancer screening age extension to 70-74 years.

Healthcare professionals have a duty of care to take reasonable steps to avoid harm to their patients. This includes informing patients of material risk that could alter their decision making. The Health and Disability Services Consumers' Rights code also details the right to services of an appropriate standard, in a manner that minimises the potential harm to and optimises the quality of life of that consumer.[252] However, it may be difficult to determine in advance what is appropriate and reasonable, which may be dependent on personal circumstance. These uncertainties around evidence and guidance can result in a loss of trust and be damaging to the relationship between patient and health professional.[247]

9 Perspectives on Breast Density Reporting

9.1 Consumer information

Breast density information has become more widely available for both patients and healthcare professionals with a primary source of this information being online resources. A 2022 review by Nickel et al. of online information about breast density available in five English-speaking countries concluded that information is not generally presented in a manner that is easy to understand or act upon and there is no consistent pattern of content. The majority of information was based on what breast density is, how it is measured and what dense breasts mean. Only a few websites directly stated benefits and harms of measuring and reporting breast density and these were mainly focused on the use of supplemental screening. The most common recommendation was for women to talk with their doctor, including the suggestion to discuss what breast density means for them, their individual risk and supplemental screening options. Furthermore, most websites did not include directly referenced peer reviewed data or articles. [253]

9.2 Participants

The perspectives of breast screening programme participants on measuring and reporting breast density have been studied in the USA for over a decade, and more recently in England and Australia There is no published evidence on participants' perspective on breast density in Aotearoa New Zealand. As discussed earlier there are differences in funding models and population stratification across health systems that could potentially influence participant and professional perspectives, however, the international evidence provides insights and can inform the approach for exploring the perspectives of BreastScreen Aotearoa participants on breast density reporting.

Breast density notifications vary by screening programme. In the USA current regulations stipulate that patients receive the classification of dense or non-dense, (where dense is defined as BI-RADS category C or D) and notification that dense tissue makes it harder to find breast cancer on a mammogram.[254] Breast Screen Western Australia notifies women when a mammogram shows marked increased breast density and they are advised in writing to consult their GP to discuss the significance of their breast density, to have a clinical examination and receive further advice about their breast cancer risk.[228] Breast Screen South Australia provide the BI-RADS density category A-D in the patient results letter.[24] BreastScreen New South Wales provide participants and their nominated GP a density report in their screening result letter, which is accompanied by a breast density factsheet.[229]

Do people want to be told their breast density at screening?

The majority of women involved in studies based in the USA and Australia would like to know their breast density.[253,255–257] Women participating in online focus groups in two Australian states that do not have breast density notification had a two-hour facilitated discussion with trained moderators about breast density. Following this, many felt that they had a 'right to know' about their breast density and they would like to be informed and educated about it.[257] Prior to this, most had not heard of breast density or did not know what it meant. It was noted that the concept of breast density and implications of having dense breasts can be difficult to understand when first learning about it. Some women argued that as breast density impacts the sensitivity of the test, women should be told about density as a routine part of the screening process .[257] They viewed provision of health information as intrinsically valuable, irrespective of whether that information can improve outcomes. A similar positive attitude to breast density reporting was found in a survey of 6922 women in Western Australia, in which two thirds of women felt that knowing their breast density made them feel more informed.[258]

Similarly, women in the USA felt more informed by knowing their breast density. In a 2017 survey of 1502 women from states with and without breast density notification legislation, 63% of women wanted to know their breast density, which had increased from 60% in 2012.[259] Forty-five percent of participants thought that receiving breast density information would create anxiety and 40% thought it would cause confusion but 90% felt they would be better informed.

Studies suggest that although breast density notification increases anxiety, women value having this information. In a survey of 264 women (48% black, 35% Latina, 17% white) in New York City where women with dense breasts were notified, 40% of the respondents said they would feel anxious if they were told they had dense breasts but the majority (77%) also felt they would be in a better position to make decisions about their health .[260] When told that doctors and scientists do not agree on the benefit of having additional tests in the context of dense breasts, 82% of participants said that they would still like to know whether they had dense breasts or not. In a study of Hispanic women in New York City attending breast screening when density notification was mandatory, most appreciated learning about their breast density and thought that this would influence future screening and help cope with any future breast cancer diagnosis.[261]

A study in the USA undertaken prior to a law mandating breast density notification in April 2013 explored attitudes to breast density reporting by women in an affluent and a more deprived area.[262] Most women wanted to know their breast density, with a higher proportion in the women attending the facility that was in a more affluent neighbourhood (94%) compared with those attending the hospital that was in a more deprived area (79%).

The majority of women would like to know their breast density, even when they were advised that there was uncertainty about the benefit of additional tests. Knowing their breast density made women feel more informed and better able to make decisions about their health.

What is the psychological impact of breast density notification for participants?

A systematic review of the impact of breast density notification on cognitive, psychological and behavioural outcomes found that women experienced anxiety and confusion related to breast density notification.[263] Anxiety could be caused by various issues: misinterpretation and misunderstanding of the information, uncertainty about what to do with the information, and from the psychological impact of increased cancer risk.[263,264] Additionally, breast density notification increases supplemental screening uptake, with a subsequent rise in false positive findings.[265] The additional screening and unnecessary biopsies can cause psychological and physical harms. In a study in Western Australia, anxiety was higher among those informed about breast density for the first time compared with those who had been notified multiple times.[258] Confusion was caused by the lack of evidence about what to do if you have dense breasts. [258]

A randomised controlled trial set in Australian states without breast density notification illustrated that informing people of their breast density causes more anxiety and confusion than not informing them. Participants receiving mammogram results were randomly assigned to either not receive breast density results, to receive their breast density results with a standard information leaflet or to receive their breast density results with a health literacy sensitive version of the information leaflet.[266] Compared with the control group, more women who received density notification via the standard information leaflet and the health literate version reported feeling anxious (14.2% vs 49.4% and 48.5%; $P < .001$), confused (7.8% vs 24.0% and 23.6%; $P < .001$), and worried about breast cancer (quite/very worried: 6.9% vs 17.2% and 15.5%; $P < .001$). There were no statistically significant differences in the above outcomes between the groups that received the standard or the health literacy sensitive information leaflet.

Australian women participating in an online focus group were asked to imagine being told they had dense breasts, and then to state what their level of anxiety would be: 30% said they would not feel anxious at all, 50% would feel a little anxious, 13% moderately anxious and 5% very anxious.[264] When asked what they would do if they were told they had dense breasts, (participants could respond with more than one option) 39% said they would talk with their doctor/GP, 23% that they would have supplemental screening, 15% said they would have annual mammograms and 19% that they would do nothing differently. Dench (2020) noted that women who reported anxiety following breast density notification had increased intention to screen in the future.[258]

In a systematic review of breast density notification in racial and ethnic groups, eight of the studies (all in the USA) examined emotional reactions to breast density notification.[267]

Seven studies reported increased anxiety among Black, Hispanic and Asian women compared with White women while one study found no difference in anxiety by ethnicity.[268] Anxiety was partly attributed to factors other than ethnicity such as reported discrimination, income and education.[269] High income women in the USA reported less anxiety about breast density notification and black women reported higher anxiety and confusion.[270] Anxiety was created for Hispanic and Spanish speaking women through difficulty understanding breast density notification[271] and concerns around the need for further screening and potential barriers.[261]

In a USA telephone survey of a diverse sample of 1322 women who had received breast density results, the level of anxiety varied by ethnicity and sociodemographics with non-Hispanic Black, Asian, and Hispanic women and women with low literacy being two to three times more likely to report anxiety than non-Hispanic White women.[272] Asian women and those with low literacy did not feel as informed and more often felt confused.

Informing women of their breast density at mammographic screening can cause anxiety and confusion. Studies from the USA indicate that this happens to a greater extent in black, Hispanic and Asian women and in those with lower health literacy. Health literacy can be viewed as a quality of the relationship and communication between a patient and their health care provider[69], which needs further exploration in the Aotearoa NZ context, particularly given recognition of the underserved population sub-groups. [273]

What formats of communication are most effective?

Breast density will be a new concept to most women, therefore effective communication of the results is critical. Some Australian women felt that breast density results should be communicated by health professionals so the results could be put in the context of other risk factors for breast cancer and any anxiety or concerns addressed.[274] Others were happy with breast density results being given by letter, and stated that this should also include an explanation of the implications of the result. Some wanted the option of having a trusted healthcare professional to discuss the results with.

A USA telephone survey of 2306 women with in-depth interviews of 61 participants concluded that a multimodal approach to density notification (e.g. letter and option to speak with a healthcare professional) was preferable and that a ‘one size fits all’ approach to breast density education will not work.[275] The majority (80%) of survey participants said that they would prefer to receive their breast density information from a healthcare provider, 12% said in a letter and 7% from a website or online portal. Preferences varied by ethnicity with a high proportion (85%) of non-Hispanic black women preferring to receive the information from a health care provider. The qualitative part of the survey found that receiving a letter accompanied by some pictures would be helpful, as was having the option to talk with a healthcare provider. Women surveyed in Massachusetts seven months after the implementation of breast density notification agreed with the need

for healthcare professional input, and stated that breast density information should be provided in the context of a woman's overall risk. [276]

Nearly all participants in a qualitative study of breast density notification among Hispanic women in the USA stated that healthcare providers are the most appropriate providers of information about breast density and several stressed the importance of an in-person discussion.[261] They also wanted an information leaflet alongside written results.

Breast density reporting commenced in Western Australia in 2008 and women with dense breasts are advised to discuss their result with their GP. Women diagnosed with interval cancer in Western Australia between 2011 and 2020 suggested that screening programmes could offer better education in a clearly understandable format about the limitations of mammography.[277] The research identified that the role of the breast screening programme in the management of breast density is a major concern, with conflicting views among participants. Some women suggested that if dense breasts are found, there should be more emphasis on the recommendation to see a GP. Others stated that they were grateful for the letter advising about their dense breasts and the potential implications and attributed earlier detection of their cancer to the letter.

A study testing the acceptability of videos that simulate face to face conversations with a computer-generated counsellor to deliver breast density information found that while there is potential for technology-based interactive solutions, there is potential that some concepts will not be understood.[278] The study found that breast density is not an intuitive concept for most women, with many participants struggling to understand what breast density is (the amount of fatty tissue relative to connective tissue).

As a minimum, breast density results need to be given alongside information about what they mean, what women should do about them and what services are available to them. Many women also wanted the option to speak to a healthcare provider who could explain the results, contextualise them within the person's overall risk of breast cancer and explore any concerns.

Does breast density notification lead to a change in behaviour for those given the results?

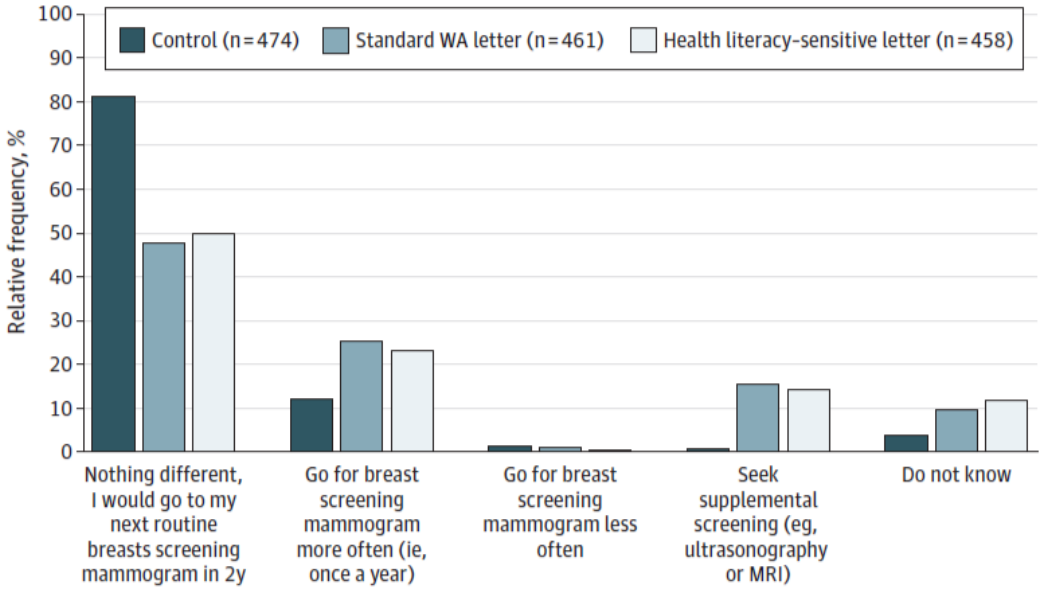
Studies in Australia suggest that some women who are told they have dense breasts would seek supplemental screening, while others would prefer to make plans based on their overall breast cancer risk. Women living in Australian states without breast density notification, were asked to consider how they would feel if they were told they had dense breasts.[274] Three main perspectives emerged: women would be alert but not alarmed (most common response), women would have supplemental screening for peace of mind, or women would not change anything. Many women felt that they would rather be over-diagnosed than under-diagnosed, with a preference for more frequent mammograms or supplementary screening if they had dense breasts.[274] Others were uncertain or felt that

they wanted more information about other risk factors before making decisions about further screening. In a scenario about supplemental testing for a woman with dense breasts, participants viewed financial considerations as one of the major determinants of the decision.[274]

Evidence from Australia suggests that reporting breast density will put additional pressure on health services. Half of the women in Western Australia who were informed they had dense breasts consulted or intended to consult their GP.[279] This was higher for women notified for the first time (55%). Of those who consulted their GP, 50% were referred for supplemental screening. Overall, of those women notified of dense breasts, 20% (550 women) had an ultrasound due to breast density.

A randomised controlled trial set in Australian states that did not usually report density sought to assess the effect of provision of breast density results on women's intentions to seek supplemental screening. Compared with the control group, women who received density notification via the standard information leaflet and the health literate version reported a significantly higher intention to seek supplemental screening (0.8% vs 15.6% and 14.2%; P < .001) or intention to attend breast screening mammography more often (12.4% vs 25.4% and 23.4%; P < 0.01).[266] For about half, receiving notification of breast density would not change their course of action (Figure 6), and very few would go for screening less often (<2%).

Figure 6: Screening intentions after receiving mammogram results. The control group did not receive breast density results.



Source: Dolan et al. 2022[266]

Women's intention to pursue additional screening in relation to breast density information was studied in a systematic review containing 13 studies (11 from USA, one from Canada and one from Australia).[263] Most women intended to have further screening. The knowledge of false positives, overdiagnosis and potential need to pay did not greatly affect this intention. However, another systematic review looking at the impact of breast density notification on psychosocial outcomes for racial and ethnic minorities found a difference in the uptake of supplemental screening for ethnic minority groups.[267] Although racial and ethnic minority groups expressed similar or increased motivation as White women to have supplemental screening, studies from before and after breast density notification legislation showed that they were less likely to undergo the supplemental screening. Suggested barriers (extrapolated from known barriers affecting communication with healthcare professionals) were socioeconomic factors, health literacy, language barriers, medical mistrust, and actual or perceived discrimination.[280] Further, healthcare professionals in the USA were less likely to order supplemental imaging for Non-Hispanic Black and Hispanic women than non-Hispanic White women (OR 0.38 [95% CI 0.17-0.85] and OR 0.24 [95% CI 0.10-0.61], respectively, $p < 0.0001$), controlling for patient age, ordering healthcare professional specialty, insurance, BI-RADS score, breast density, and family history of breast cancer. [281]

Uptake of supplemental screening in the USA is affected by many factors including ethnicity and socioeconomic status. A systematic review of the impact of mandatory mammographic breast density notification on supplemental screening practice found that patient-level factors such as previous breast biopsy, family history of breast cancer, higher socioeconomic status, ethnicity, age and breast density were associated with supplemental screening uptake.[282] In a national survey that included women's intentions if they were notified about having dense breasts, uptake of supplemental tests was lower for women of lower socioeconomic status and ethnic minority women.[270] There was high interest in supplemental screening with ultrasound in a deprived rural area and a more affluent urban setting (73% and 94% of women respectively expressed interest in supplemental screening).[262] However, only 22% of women attending the more deprived rural hospital would be willing to pay for this supplemental screening, in contrast to 70% of women attending the more affluent urban centre

A USA telephone survey of women who had received breast density results found that overall 30% would be more likely to have future mammography and 2% less likely.[272] The rest had unchanged plans. This varied by ethnicity with 39% of non-Hispanic Black women, 37% of Asian women and 24% non-Hispanic White women indicating they were more likely to have future mammograms. Each women's breast density was not established, and this could have impacted on people's intentions. Women with lower levels of anxiety were less likely to change their future screening plans, whereas those with higher levels of anxiety were more likely to report changes to their plans for future

mammograms in both directions – some more likely and others less likely to have a future mammogram.

A study in the USA illustrated how the manner of notification impacts the uptake of supplemental screening.[283] Less than half (49%) of women who received written notification of breast density attended for follow-up ultrasound scan whereas 87% who also received a phone call had an ultrasound scan.

These studies indicate that there are likely to be significant healthcare resource implications as a consequence of reporting breast density, in terms of reporting and explaining the results and for additional imaging. In Western Australia, half the women with dense breasts consulted or intended to consult their GP and 20% of the women with dense breasts had an ultrasound scan due to breast density. American studies indicate equal intentions but lower uptake of supplemental screening by women of racial and ethnic minorities, as well as by women with low socioeconomic status. Therefore, there is the potential for breast density notification to further disadvantage minority groups and breast density information needs to be carefully considered to ensure understanding by all women.

There is no published evidence of the opinions of breast screening participants in Aotearoa New Zealand on reporting breast density, however, Aotearoa New Zealand breast cancer organisations Breast Cancer Foundation NZ and Breast Cancer Aotearoa Coalition are in favour of breast density being reported by BreastScreen Aotearoa.[284] It would be useful to understand if women participating in BreastScreen Aotearoa have a similar perspective to breast density reporting as women in Australia and the USA, and what their intent for supplemental screening may be.

Disability Perspectives

Pre-existing disability is associated with a higher likelihood of breast cancer diagnoses.[285,286] There is currently no specific literature on the perspectives of disabled people and reporting breast density, however, review studies and meta-analysis have shown that women with disabilities face disparities in receipt of preventative cancer care.[287] Disparities in mammography breast screening vary by disability type and severity, and grow over time.[287–289] Increasing complexity of disability and other factors such as ethnicity, rurality and socioeconomic status can compound to further lower rates of screening for those with disability.[289–291] International studies have identified a number of barriers that contribute to poor breast screening participation. These include physical barriers such as; access, cost/insurance, accommodations, communication, social and professional support, as well as intangible barriers such as being appropriately informed, involved, treated with respect and maintaining control.[292–294] Women with a disability are less likely to receive a healthcare professional's recommendation for mammography screening[295] and there are concerns around women with intellectual disability providing informed consent.[296] Approaches to reduce disparities in breast cancer screening for

women with disabilities should focus on improving accessibility by removing physical barriers like mobility and access to screening centres, equipment, and healthcare facilities. Healthcare professionals require support and education on preventive care for patients with disabilities and regulatory bodies should focus on overcoming socio-economic barriers to equally dispense the national policies across social, ethnic, and economic strata.[289]

9.3 Perspectives of Healthcare Professionals

Studies from the USA, Australia and England provide evidence on the knowledge, thoughts and concerns of healthcare professionals on breast density reporting. Despite the differing settings (health system structure, presence or not of breast density notification), common themes emerge from the studies: variable knowledge about breast density, a desire for more education, uncertainty over what to advise a woman with dense breasts, the need for national guidelines on breast density including the role of supplemental imaging and putting breast density in the context of other risk factors for breast cancer. The known perspectives of GPs/Primary Care Physicians, Radiologists and Breast Surgeons on breast density measurement and reporting are discussed in greater detail below.

General Practitioners / Primary Care Physicians

Two studies in Australia examined General Practitioners (GPs) attitudes to breast density reporting. Interviews of 30 GPs by telephone (including three participants from Western Australia, the only state at the time reporting breast density). Overall, the GPs felt they had a low level of knowledge about breast density and needed training. Many had concerns about how to communicate breast density information to women. Some GPs expressed uncertainty as to how much risk dense breasts confer and were concerned there were no clear guidelines on management. However, they felt that women should be able to make informed decisions and some suggested that knowing about breast density and its implications may make women more vigilant and proactive. They discussed the importance of being open, even in the context of substantial uncertainties. Some felt there was benefit in women with dense breasts consulting with their GP, who can take into account other risk factors, which could inform discussions about the possible benefits and harms of supplemental screening.[263]

A survey conducted in 2021 of 60 GPs from various states in Australia, including 11 GPs from Western Australia, found that generally GPs had a positive perspective on breast density reporting.[266] Most GPs (87%) had experience with discussing breast density with patients. There was strong support (75%) for breast density to be reported to women and 76% agreed or strongly agreed that notifying women of their breast density would promote informed decision-making. There were varying approaches to offering supplemental screening, with the patient's overall risk of breast cancer being the most influential factor in

decision making. Over three quarters of the respondents (78%) felt that they needed more education on breast density. Most GPs (92%) felt that women have the right to know their breast density, noting that 52% felt that this information may cause undue anxiety. The authors note that their study contained a high proportion of GPs with an interest in women's health and/or breast health (35%) and that GPs who had taken part in the survey might have a particular interest in this topic and not be representative of all GPs.

Six studies from the USA were included in a systematic review of the impact of breast density notification on GPs.[263] Five studies were in states post breast density notification and one in states both pre- and post-legislation. There were mixed views about breast density notification laws. GPs expressed positive attitudes about how the legislation might affect patient engagement. However, they were concerned about the lack of evidence informing next steps for screening patients with dense breasts and about causing stress and anxiety. Similarly to Australian GPs, American GPs wanted to contextualise breast density into a broader conversation about risk factors for breast cancer and were particularly interested in discussions about modifiable risk factors such as exercise and alcohol intake. American based GPs also wanted more education and training around breast density.[263,265,297]

Radiologists

On the whole, radiologists in the USA had a more negative perspective of breast density notification than GPs, with concerns regarding the lack of evidence on supplemental screening and creating additional work for providers and worry for patients.[276] In terms of discussing breast density results with participants, some radiologists thought it best done by GPs who were well positioned to assess all the risk factors, others thought a combined approach best and others that it could be done by a non-clinical person such as a health educator.

Breast density knowledge among radiologists in the United Kingdom (UK), where breast density is not reported, was quite variable.[298] In a survey of 123 breast radiologists, 16% were not aware that the accuracy of mammograms is affected by breast density and 47% were not aware of the relative risk for breast cancer by degree of breast density. Half the radiologists said they would offer supplementary screening to women with dense breasts, with the most common choice being tomosynthesis, followed by MRI, then ultrasound. Over half (59%) were concerned that routine supplementary imaging could result in overdiagnosis.

Breast surgeons

All of the breast surgeons who responded to a survey on breast density (109) in the UK stated that they were aware that mammographic accuracy is affected by breast density.[298] Less than half (40%) shared breast density information with their patients, with the most common reason for this being that they do not feel this information should be shared if no

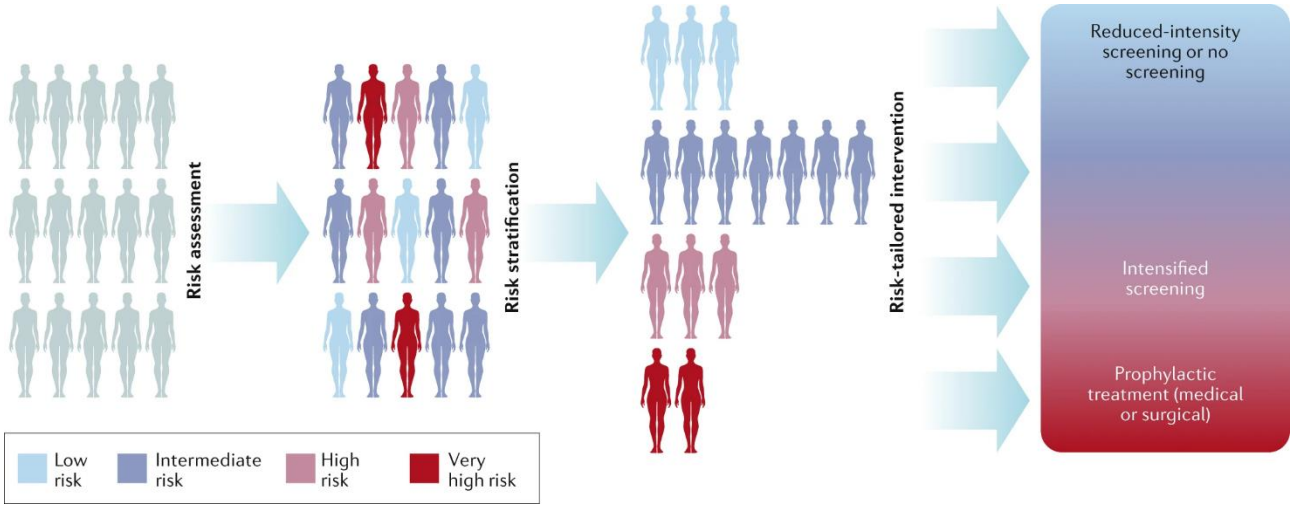
alternate imaging is offered, followed by some not having breast density information available, some having time constraints and a few not feeling confident to discuss it. Just over a third (36%) routinely offered further imaging to women with increased breast density, with MRI being the most common, followed by ultrasound. It is not clear from the paper in what context the surgeons were considering mammograms and breast density: it may be at the assessment stage of the screening pathway. Ninety percent agreed that there was need for further guidelines on the management of breast density.

10 Broader Risk Stratification Approaches

There are multiple factors including breast density that are known to increase breast cancer risk for women. However, evidence on how to identify, screen and manage women in high-risk groups within current programmes is still unclear. Risk stratification or risk-based screening protocols use risk assessments and screening technologies to provide personalised screening protocols that vary depending on the overall risk.

As described by Figure 7 below, women entering a personalised screening programme would initially be assessed using a validated tool to calculate their estimated risk of breast cancer. Subsequently, women would be stratified into risk groups such that they can receive tailored interventions. This approach might mean that some women start mammographic screening at a younger age, have different screening intervals or have supplemental screening with another imaging modality, such as MRI. Women deemed to be at higher risk of breast cancer could, in addition, be offered prophylactic treatment. A healthy lifestyle would be recommended to all women, independent of risk level.[299] As discussed in section 6. Risk Assessment Tools, there are limitations with using an appropriate tool.

Figure 7: Schematic outlining a personalised approach to early detection and prevention of breast cancer



Source: Pashayan et al.[299]

10.1 Research on Risk Stratification Approaches

The Roadmap to Optimising Screening in Australia (ROSA) project was established in 2018 to explore risk-based breast cancer screening specifically for Australia. Clinical and economic modelling based on local data indicated that different risk profiles for the current target age range of 50-74 years from 2025 could reduce population level breast cancer mortality by up to 7% (873 lives) in the first 10 years of implementation, with further reductions possible if extended to younger age groups. Risk-based screening could reduce the worse prognosis diagnosis by up to 20% in the higher risk group and consequently reduce treatment intensity. Interval cancer rates in the high-risk group could also be reduced. Conversely, the proportion of invasive screen detected cancers that are overdiagnosed could increase by up to 50%. This model allocated 20% of women to the higher risk group and this was the group expected to benefit most from risk-based screening. Based on this modelling and other key findings the ROSA project recommended a set of activities to guide and support implementation of risk-based screening in the Australian context. Activities include an initial review of policy and guidelines to develop consistent advice with planned co-ordination and data sharing between health services, clinical studies to support the design of a locally based clinical trial, with ongoing enhanced data collection, linkage, monitoring, targeted reviews, consumer and stakeholder engagement as well as engaging in research that addresses evidence gaps.[220]

Currently there are six population-based clinical trials underway that have been designed to assess the benefits and harms of various risk-based breast cancer screening protocols. These are summarised in Table 7, with further details in the Appendix.

Table 7: Population level trials of risk–based breast screening

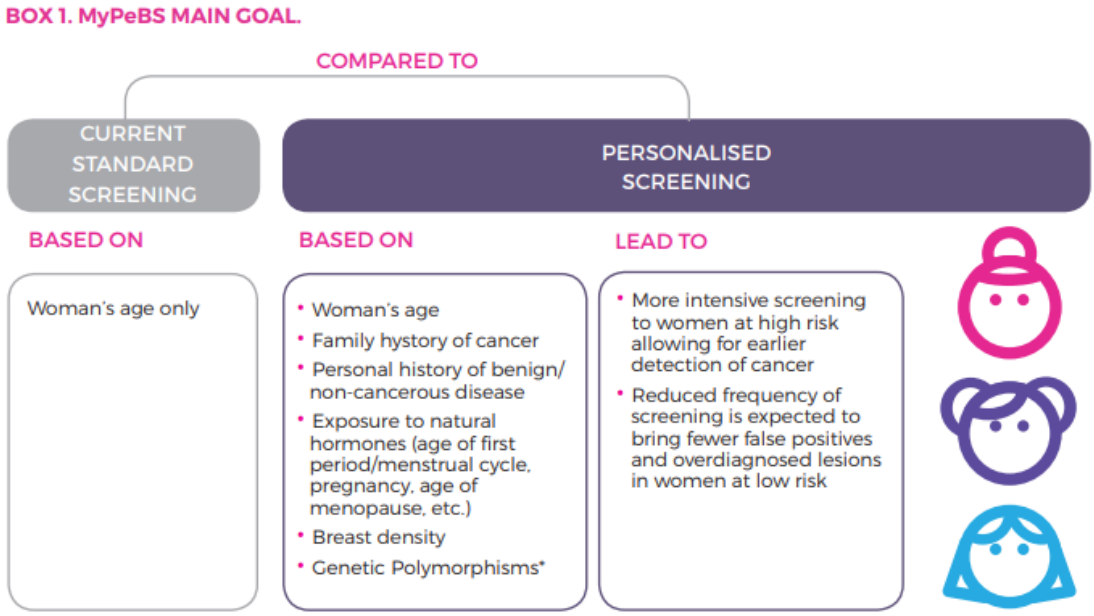
Trial (age range)	Location	Trial period	Risk groups	Risk Tool	Comparator	Intervention	
						Intervals	Supplemental screening tests
MyPeBS – My Personal Breast Screening (40-70)	France, Italy, UK, Belgium and Israel	2019 - 2025	BCSC/Tyrer-Cuzick scores (4 groups)	Algorithm incorporating BCSC score, Tyrer-Cuzick score and genotyping	Various (Annual/biennial/triennial screening, with mammography/ DBT± supplemental US)	1-4 years	**US, MRI**
WISDOM - Women Informed to Screen Depending on Measures of Risk (40-74)	USA	2016 - 2020	BCSC score (4 groups)	BCSC model and genotyping	Annual mammography	1-2 years None <50y	**MRI**
TBST - Tailored Screening for Breast Cancer in Premenopausal Women (45-50)	Italy	2013 - 2022	BI-RADS 1-2 versus 3-4	Breast density (BI-RADS classification)	Annual mammography	2 years for BI-RADS 1-2	**N/A**
DENSE - Breast Cancer Screening With MRI in	Netherlands	2011 - 2019	Extremely dense (Volpara D)	Breast density (Volpara grade 4/D)	Biennial mammography	No change	**MRI**

Trial (age range)	Location	Trial period	Risk groups	Risk Tool	Comparator	Intervention	
						Intervals	Supplemental screening tests
Women With Extremely Dense Breast Tissue (50-75)							
BRAID - Breast Screening – Risk Adaptive Imaging for Density Cluster-RCT (50-70)	UK	2019 - 2026	BI-RADS C-D	Breast density (BI-RADS classification C/D), excluding BRACA mutation	Triennial mammography	18 months	**Abbreviated MRI, US, CEM**
MISS - What is the Best Interval to Screen Women 45-49 for Breast Cancer (45-49)	**Italy**	**2020 - 2026**	**BI-RADS A-C versus D.**	**Breast density (BI-RADS classification)**	**Uncertain (most likely annual tomosynthesis)**	**2 years for BI-RADS A-C**	**N/A**

Four of these trials are designed to assess whether risk-based screening, where screening intensity is reduced for some women, is not inferior to standard programmes where women are generally all recommended the same screening protocol. The MyPeBS and WISDOM trials aim to determine if personalised screening based on a 5-year estimated risk of breast cancer (refer figures 8 and 9), is not inferior to standard country-specific age-based screening practices with respect to the rates or proportion of stage 2B or more advanced cancers. The WISDOM trial will also investigate if biopsy rates are lower with personalised screening. The TBST and MISS trials aim to assess the impact of biennial

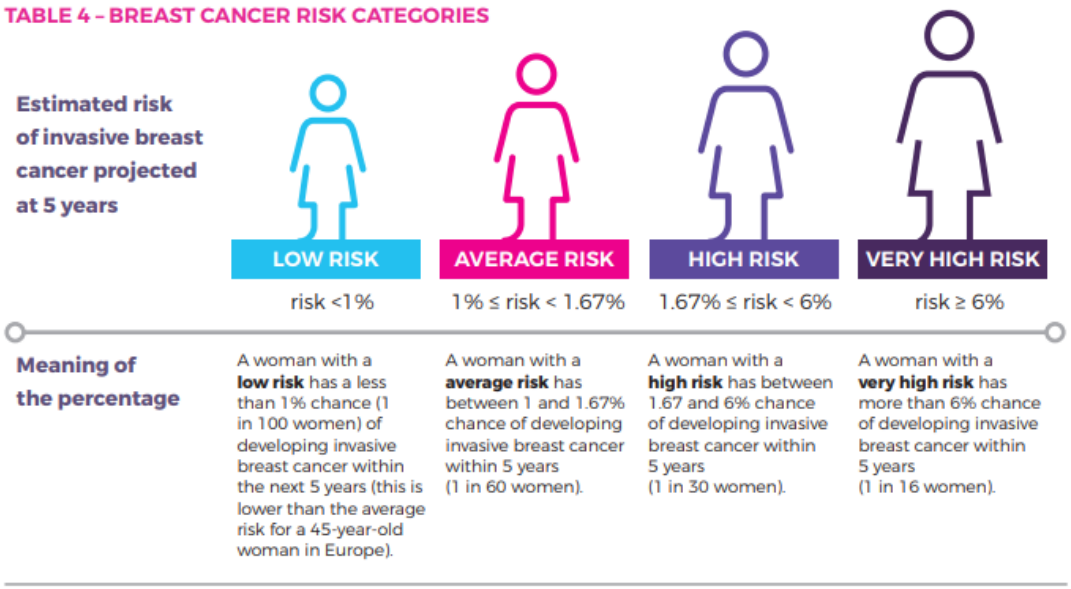
rather than annual screening for premenopausal women with lower breast density, on the incidence of interval cancers (TBST) or more advanced cancers (TBST and MISS).[300]

Figure 8: MyPeBS Screening options



Source: MyPeBS Questions and Answers301

Figure 9: MyPeBS Risk Categories



Source: MyPeBS Questions and Answers[301]

The DENSE and BRAID trials are designed to assess if the addition of supplemental screening for women with denser breasts improves outcomes within standard screening programmes. The DENSE trial aims to assess the effectiveness of offering MRI in addition

to mammography to women with extremely dense breasts. The interval cancer rate for biennial screening with and without supplemental MRI will be compared for women with extremely dense breasts (>75% mammographic density). The BRAID trial is designed to investigate whether breast cancer detection rates will improve when women with dense breasts (BI-RADS C or D) are offered supplemental imaging in addition to three yearly standard screening. There are three intervention arms where women with dense breasts receive additional mammographic screening at 18 months and supplemental imaging at baseline and at 18 months using one of three imaging modalities; either abbreviated-MRI, automated whole breast ultrasound or contrast-enhanced mammography. The trial aims to assess the different modalities of supplemental screening as well as the effect of providing both supplemental screening and more frequent screening for women with dense breasts compared to standard triennial mammographic screening.[300]

Clinical trials are the best evidence for protocol development, however, mortality outcomes take time to assess and only a limited range of protocols can be evaluated. Modelling studies have been used to estimate costs, benefits and harms of risk-based screening strategies. Lower breast cancer mortality and improved quality of life was predicted for women at higher risk if screened more frequently and from a younger age.[302,303] These benefits however would come at the expense of increased false positives and overdiagnosis[303],although, less intensive screening of lower risk women could reduce false positive rates in this group .[302] Cost-effectiveness of screening strategies is context specific and hard to compare between studies, with some reporting that risk-based screening would be more cost effective than uniform screening for all women whereas others did not.[302–306]

10.2 Limitations and considerations of risk stratification

Ideally, risk stratification should use risk factors either strongly negatively or positively associated with the screening condition and should not be highly correlated with one another.[307] In reality, this is population dependent and risk factors are often related (for example, diabetes and weight as risk factors for colorectal cancer).[307] Any stratification will need internal validation but importantly, it will need external validation in the context for which it is being considered.[307,308] Many risk stratification models and approaches are in the research stage. Success in a research setting does not necessarily imply clinical utility or improvement in outcomes.[308] Cost effectiveness in different settings is also critical as there will always be associated capacity constraints and considerations (for example, the use of MRI for individuals at high-risk of breast cancer).

Screening programmes must be acceptable to all involved if they are to be successful and it is particularly important that uptake and application do not compound inequities.[308] A recent systematic review discussed acceptability of risk stratification in cancer screening from a healthcare providers perspective.[309] Only 7 out of 12,039 papers were considered suitable for review, perhaps reflective of a gap in the literature, with 6 focusing on breast

cancer screening.[309] However, the authors concluded the findings were broadly consistent with evidence on the attitudes of the general public to stratification. They describe risk stratification as acceptable in principle to healthcare providers and the public – with evidence that the public is 'largely optimistic about risk stratification'. It is seen as a sensible way to address benefits and harms, but successful implementation would need to address a number of concerns.[309]

Development and use of risk stratification approaches is resource and personnel intensive. Alongside education, awareness and communications, IT, intelligence, and personnel will need to be considered from the outset.[310] This includes ensuring perceptions of risk stratification approaches, particularly the interpretation of risk, by patients and healthcare providers is understood and considered.[309] Taylor et al., emphasise that "for healthcare providers to find risk-stratified cancer screening acceptable, it is essential to understand whether it is acceptable from the perspective of the general public".[309] Engaging the public throughout development and implementation will be critical to successful use of any risk stratification.[307,309]

Even though reduced screening for low-risk women presents an opportunity for equivalent outcomes, the potential reduction was highlighted as a concern and would need effective guidance and supportive resources. Similarly, clarity around the management of moderate risk individuals was felt necessary.[309] For healthcare providers to use risk stratification appropriately requires a good understanding of the assumptions and rationale behind it.[308–310] Without this, there is the risk of incorrect or inappropriate use and to cause harm.[308] Training and education would be critical and for change to become embedded and new processes used appropriately, this would need to be repeated and long-term.[309]

The cognitive load, and time required, on already stretched providers, particularly in primary care, needs to be considered.[309] This includes the responsibility for the use and interpretation of any risk stratification, and decisions on risk management where required. Any tools would need to be well integrated with existing electronic patient management systems, require easily available input data, and be simple, quick, and routine.[308,309] However, their use would almost certainly require increased time and support for patients. The current breast cancer risk stratification is complex and primary care providers are strongly encouraged to collaborate with specialist breast care providers and geneticists. Managing this and the needs of the individual, who may have significant psychosocial concerns, takes considerable time in a primary care setting that is currently time poor. Capacity and funding requirements would need to be carefully considered during the development and planning for risk stratification amendments to screening programmes. There is risk that the increasing complexity of health information, particularly around the concepts of risk stratification and breast screening compared with investigation of symptoms, in the absence of appropriate guidance / recommendations has the potential to increase inequities. Having clear, accessible communication including explanation of breast cancer risk for the public and for providers would be critical to ensure adequate

informed consent and to support equity.[309] This would include ensuring uniform guidance with evidence-based clinical guidelines that are consistent with national policy.[309] Currently, primary care providers use Community Health Pathways, with district level variation in these including variation in the guidelines for management of individuals at high-risk of breast cancer.

Cost effectiveness in different settings is an important consideration but Taylor et al., emphasised that whilst cost-benefits were seen as important, the health benefits must be seen to be the priority - when communicating the cost-benefits to the public, policymakers should be careful not to undermine these.[309]

Additional risks include at an individual level with the potential for increased anxiety, or being put off routine screening once 'labelled' as either high or low risk. Those considered low risk may be less likely to address modifiable risk factors. Communicating risks in a meaningful way is resource intensive at an individual and population level and it is imperative inequities are not exacerbated.[311]

Data access, including coded data, for development of algorithms requires large data sets and continued access to this data will be required to evaluate and inform future programmes.[310] There may be data collection, sharing and storage implications, and in Aotearoa New Zealand data sovereignty is an important consideration, particularly for Māori. Institutions will need to collaborate and to have clear policies and procedures, including for data sharing and use.[310]

Genetic data is increasingly used, with particular privacy, storage, and access considerations.[310] It is important that genetic data adequately represents the population for whom any risk stratification algorithm is to be used. This is particularly important for ethnicity – with minority ethnicities often under-represented. It is critical that risk stratification models recognise and allow for this to ensure equitable utility.[310]

It is also important to ensure that the risk stratification models used are adaptable. For example, an individual may change lifestyle behaviours through their life course and their risks may need re-classifying.[310,312] Similarly, understanding and interpretation of genetic risks will change as knowledge increases. New treatments will also need to be considered with stratification levels amended where appropriate.[310] With this adaptability, there is the need to consider the ethical rights of individuals to be informed of any changes, and the communication required to support this.[310]

11 Discussion

11.1 Key findings in relation to current knowledge

Women with higher breast density have an increased risk of developing breast cancer compared to those with low breast density and are more likely to have a breast cancer missed on mammography. BreastScreen Aotearoa does not currently measure breast density, therefore, the relative distribution in Aotearoa New Zealand women is unknown. Measurement in an appropriate cohort would be required to accurately estimate the number of women in Aotearoa New Zealand with dense breasts, with international studies suggesting up to half of the female population could reach the threshold of moderate to high-risk density. Breast density can be determined by a radiologist through visual assessment of mammography images or through automated breast density reporting tools e.g. AI. These both come at a cost of radiologist time or IT investment respectively.

Internationally, and in Aotearoa New Zealand, supplemental breast screening has been recommended for women deemed to be at high-risk of developing breast cancer. Although evidence for this is growing, particularly in terms of improved cancer detection and reduced interval cancers, mortality benefit has not yet been demonstrated and may be modest.

Supplemental screening options including MRI, ultrasound and CEM have been shown to increase the detection of cancer compared to standard mammography. All methods are associated with varying benefits and risks. MRI has the greatest sensitivity for breast cancer detection but comes with an increased false positive rate and is a costly procedure. Ultrasound is not as sensitive as MRI and has a similar false positive rate, however, it is a less invasive and less costly procedure. CEM is nearly as effective as MRI for cancer detection, with less false positives and is a simpler, lower cost method, however, is not routinely available in New Zealand.

Supplemental screening for women with dense breasts has been shown to increase cancer detection rates, to detect cancers earlier and to decrease the rate of interval cancers. The main harms of supplemental screening are the increase in overdiagnosis and false positives. There are also opportunity costs with potential impacts on both the existing breast cancer screening programme and symptomatic pathway.

Risk-based screening protocols use risk assessments and screening technologies to provide personalised screening protocols that vary depending on the identification of risk. Population-based clinical trials are currently underway designed to assess the benefits and harms of various risk-based breast cancer screening protocols. Some are assessing the effect of supplemental screening for women with dense or extremely dense breasts on

screening programme outcomes, and some are assessing risk-based screening that includes reduced screening for some very low risk groups.

In Aotearoa New Zealand there is significant inequity in breast cancer outcomes, particularly related to the symptomatic pathway, but also in access to breast cancer screening. It may be that wāhine Māori have a higher proportion of dense breasts than New Zealand European/Other women, and this may contribute to inequities in breast cancer rates and outcomes. Breast density assessment is currently only available to women who have health insurance or pay for breast screening through private providers. This creates further inequities for women with dense breasts, who already may not receive the same outcome benefits from current breast screening programmes as those with less dense breasts.

11.2 Key Conclusions

Breast density is an important consideration in relation to breast cancer risk including in the breast screening context, given its association with both breast cancer risk and potential reduced accuracy of screening mammograms. As such it should be considered when evaluating a women's risk of breast cancer.

Women with higher than average risk of breast cancer may benefit from supplemental breast screening, however, currently there is no consensus on how best to manage women with dense breasts. Modelling data supports the use of risk-based screening protocols, including risk assessment tools and screening technologies, to provide personalised screening protocols that improve programme outcomes.

Overseas evidence suggests that women want to know their breast density, although this is associated with anxiety, and does vary across population groups and health care contexts. Failing to address the increased risk of breast cancer in women with dense breasts could be seen as contributing to inequities.

These issues need to be assessed in the context of the current BreastScreen Aotearoa screening programme with an aim to introduce risk-based screening in the future.

Incorporation of breast density notification into an existing screening programme is ethically complex given the lack of consensus for follow-up of women with dense breasts. Issues to consider include equitable care, patient autonomy, physician education, duty of care and uncertainties relating to measurement and clinical management pathways for women with dense breasts.

Consideration needs to be given to the best way to measure breast density within the BSA programme, including the possible use of artificial intelligence (AI) versus visual assessment by a radiologist and what the additional costs for these would be. The prevalence of breast density amongst women in Aotearoa New Zealand needs to be

ascertained to understand the potential programme impacts, benefits and costs, including the potential number of women who may be offered supplemental screening.

Further evidence from international trials is required regarding the impact of supplementary screening for women with high breast density on breast cancer outcomes (e.g. mortality) and to provide guidance on risk stratification options, screening modality and interval.

Aotearoa New Zealand specific cost-effectiveness modelling would greatly assist in providing information regarding health system and economic implications of various policy options, including alternate ways to achieve marginal improvements to breast cancer outcomes (e.g. alternate age ranges, modalities (e.g. DBT), intervals, and interventions to improve current programme participation).

The current BSA workforce capacity needs to be assessed with regards to BreastCare nurses and Medical Imaging Technologists (mammographers) potentially needing to explain breast density results and recommendations for supplemental screening with women. As does the funding and workforce enhancements that would be needed to undertake further ultrasound assessments.

The capacity of the wider health system to fulfil supplementary ultrasound or MRI requirements also needs to be assessed. CEM is not routinely available in Aotearoa New Zealand and there is limited availability of DBT. If supplemental screening is not available to women with dense breasts through the public health system, it will not be accessible to many due to cost. This is likely to further disadvantage some groups of women already facing inequities, for example, wāhine Māori with dense breasts and those living in areas of socioeconomic disadvantage.

A more detailed assessment of whole system capacity issues and potential impacts on the BSA programme in the context of current projects and existing coverage inequities for Māori and Pacific women is also required. This knowledge is necessary to produce robust local guidelines and recommendations for women with dense breasts.

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13 Appendices

13.1 Related Considerations

In this section a number of topics related to management of high-risk groups and risk stratification in screening settings are outlined to provide additional context to the consideration of breast density and risk assessment in breast screening.

Women with a high-risk of breast cancer: The example of BRCA gene mutation management

As outlined earlier in Section 5, there are a range of factors which impact breast cancer risk. The lifetime risk of breast cancer is significantly increased by the presence of BRCA gene mutations. Whilst BRCA mutations account for around 5 percent of all breast cancers, together they are responsible for over 90 percent of hereditary breast and ovarian cancers.[313,314] The estimated prevalence globally is 1:300 to 1:1000 of the general population, but this is population dependent.[314] There is no formal BRCA register in Aotearoa New Zealand and its epidemiology in Aotearoa New Zealand is not fully understood; we currently do not know how many women in New Zealand have been assessed, or diagnosed, with a pathogenic BRCA mutation.[315] The Australian eviQ guidelines report population carrier frequencies for BRACA1 and BRACA2 of 0.1% and 0.2% respectively, noting that these are approximates and do not account for population specific differences.[112]

Surveillance is the monitoring of individuals considered at increased risk of a condition and is generally of smaller scale, but increased intensity compared with screening, which effectively identifies high-risk individuals from an average risk population. The differences between surveillance and screening may not be entirely distinct, and screening organisations should work closely with those undertaking surveillance.[9]

The optimal surveillance approach for those known to be BRCA mutation carriers – including imaging modalities and scheduling – remains uncertain, particularly for younger women.[316] Currently, management varies from country to country but generally involves a combination of clinical examination, MRI and mammography, though may involve other imaging modalities such as US, DBT and CEM.[313]

Management of BRCA Internationally

Although many jurisdictions use a combination of surveillance modalities described above, there is a lack of consensus on the details - including modalities used, age of commencement and scheduling. Described below are guidelines from Australia, UK, and USA but recent reviews have described and tabulated recommendations from 19 different countries, highlighting the variance.[313,317]

Australia

eviQ Guidelines[112]: For individuals known to be BRCA mutation carriers or considered at 50% risk of being a carrier based on a validated risk assessment, surveillance should commence at 25 to 30 years of age with optimal timing determined by shared decision making and use of CanRisk (refer section 6) or equivalent.

- Under 40 years of age: annual MRI (ultrasound if MRI not available or contra-indicated)
- Between 40 and 60 years of age: annual MRI and annual mammogram (mammogram and ultrasound if MRI not possible)
- Over 60 years of age: annual mammogram (consider MRI or ultrasound if high breast density)

Note: eviQ suggests that where MRI is used there is no additional value in using ultrasound or clinical breast examination.

United Kingdom

National Institute for Healthcare and Clinical Excellence (NICE) guidelines.[318] Genetic testing should be offered to those considered 10% or more at risk of BRCA mutation or where family history criteria met.

- All individuals considered at increased risk should be encouraged and supported to be 'breast aware'.

Individuals known to be BRCA mutation carriers or considered greater than 30% risk of being a carrier should be offered:

- 30 to 49 years of age: Annual MRI and
- 40 to 59 years of age and greater than 30% risk of carriage (that is, having a BRCA gene mutation known to increase risk of breast cancer): Annual mammography with a return to routine screening at 60 years of age
- 40 to 69 years of age and known BRCA mutation carriage: Annual mammography with a return to routine screening at 70 years of age.

Consider annual mammography for:

- 30 to 39 years of age: For individuals at high-risk for other reasons but are less than 30% risk of carriage, or assessed as greater than 30% risk of carriage
- 30 to 39 years of age: For known BRCA mutation carriers in addition to MRI

Ultrasound should not be offered unless MRI is not possible, or interpretation is difficult.

USA

American Cancer Society screening recommendations for women at high-risk.[319] High-risk individuals are considered those known to be BRCA mutation carriers, or with a lifetime risk of 20 to 25% or higher or a strong likelihood of carriage based on family history, or have had chest radiation before 30 years of age:

30 years of age for as long as 'in good health': Annual MRI and annual mammogram.

They emphasise that evidence on best age for commencement of surveillance is limited and can be made on a case-by-case basis through shared decision making.

National Comprehensive Cancer Network (NCCN) guidelines.[316]

Confirmed BRCA mutation carriers:

- Breast awareness from 18 years of age
- Clinical breast examination 6 to 12 monthly from 25 years of age
- 25 to 29 years of age: contrast MRI (mammogram or tomosynthesis if MRI is not possible)
- 30 to 75 years of age: annual mammogram (consider tomosynthesis) and contrast MRI
- After 75 years of age: case-by-case basis.

They note that appropriateness of modalities and scheduling is still under study and that use of MRI depends on capacity and capability.

Management of BRCA in Aotearoa New Zealand

In Aotearoa New Zealand, there are three defined categories of risk in breast cancer – average, moderate, and high-risk. Management is guided by the Standards of Service Provision for Breast Cancer Patients in New Zealand 2013 (the Standards NZ) but there may be some regional variations in service provision for publicly funded services.[109]

Average risk is considered up to 12% lifetime risk and includes over 95 percent of the female population. These individuals are offered routine breast screening through BreastScreen Aotearoa (BSA) between 45 and 69 years of age.

If there are concerns about an increased breast cancer risk, usually based on a family history or a personal history of cancer suggestive of a BRCA mutation, a risk assessment should be undertaken, and this is generally done using eviQ.

The eviQ 'Breast Cancer referring to genetics' provides clear guidelines on individuals who should be referred to genetic services and managed by breast care specialists.[112] This

risk assessment should be undertaken by someone with expertise in interpretation which usually includes the individual's GP in collaboration with their local breast care service.

For those considered at moderate risk of breast cancer (12-25% lifetime risk) current management recommended by the Standards NZ is that:

- Individuals should be encouraged to be breast aware and to report any concerns promptly to their primary care provider.
- All individuals should have an annual clinical breast examination from 10 years prior to the age of onset for the youngest affected family relative or starting at 25 to 30 years of age.
- An annual mammogram from 40 to 50 years of age. These mammograms are fully funded with funding alternating between BSA and Health New Zealand | Te Whatu Ora. Specialist recommendation may be for a small number of moderate risk women to commence annual mammography prior to 40 years or continue beyond 50 years of age.
- Beyond 50 years of age, if breast cancer had not been identified, the individual should return to routine two yearly mammography through BSA.

Individuals considered high-risk should be referred to Genetic Health Service New Zealand (GHSNZ) for consideration of genetic testing. Referral and testing is publicly funded. GHSNZ geneticists are responsible for determining who should be tested and for what and provide the appropriate genetic counselling. eviQ guidelines recommend referral for testing at a risk of BRCA mutation carriage at 10% or higher.

For surveillance, the Standards NZ consider high-risk a lifetime risk of 25% or higher and includes those known to carry BRCA1 or BRCA2 mutation, or with a strong family history.

All high-risk individuals should be managed through a breast care service with surveillance undertaken outside of BSA but fully funded through Health New Zealand | Te Whatu Ora. Current guidelines recommend surveillance as follows:

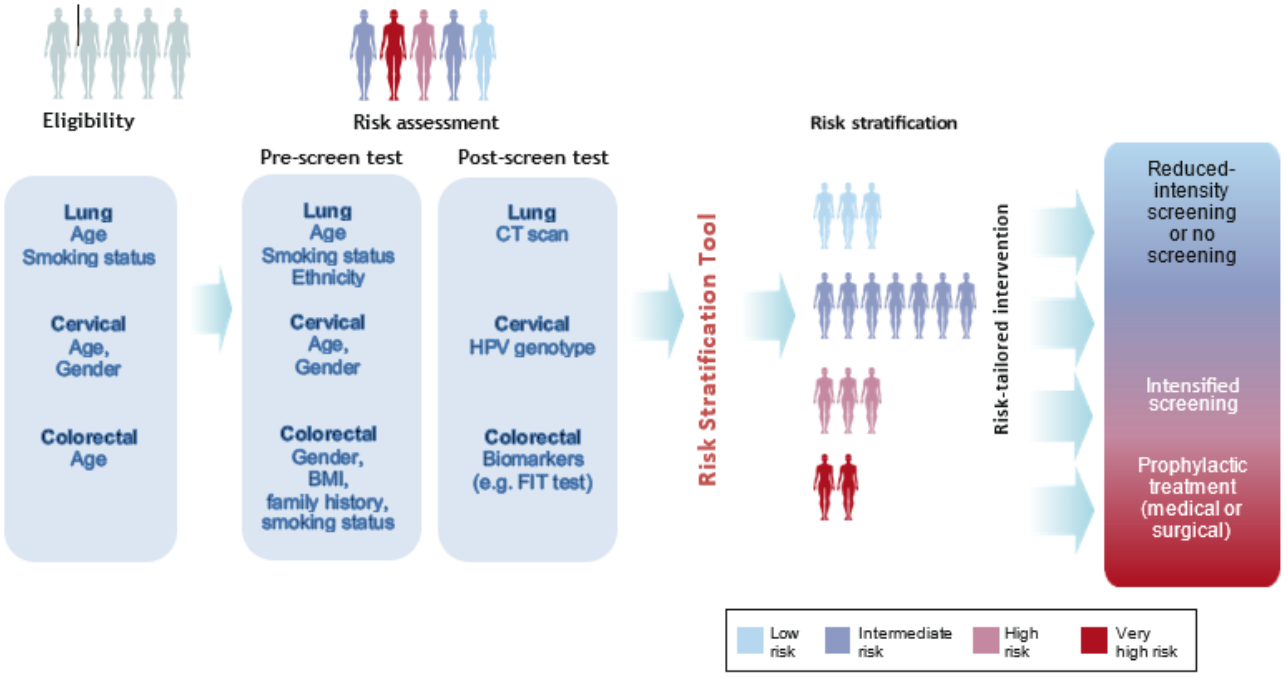
- Individuals should be encouraged to be breast aware and to report any concerns promptly to their primary care provider.
- All individuals should have a clinical breast examination every 6 to 12 months with a breast specialist from 10 years prior to the age of onset for the youngest affected family relative or starting at 25 to 30 years of age.
- Annual MRI and additionally consider annual mammography from 10 years prior to the age of onset for the youngest affected family relative. Before 30 years of age mammography is not recommended as it is less sensitive and carries a risk of radiation-induced cancer.

Although the Standards NZ do not specify an upper age cut off for surveillance, MRI is usually offered and publicly funded until 50 years of age although this may vary on a case-by-case basis or with regional variation. There is no standard in Aotearoa New Zealand for the use of digital breast tomosynthesis, ultrasound or contrast- enhanced imaging.[315]

13.2 Risk stratification in other cancer screening programmes

Risk stratification aims to modify components of the screening pathway – for example, screening eligibility, tests, and scheduling – in a systematic and reproducible way of translating population risks to individual level risk characteristics to determine personal risk. It has the potential to increase screening and target treatments for those most at risk whilst decreasing screening for those at lower risk, and in doing so deliver individual and population level benefits (see section 10 Broader Risk Stratification Approaches).[309] Increasingly, screening programmes are incorporating degrees of risk stratification to inform approaches, some of which are used in Aotearoa New Zealand and discussed further below.

Figure 10: Risk Stratification in screening programmes



Source: Adapted from Pashayan et al.[299]

Cervical cancer screening and Human Papilloma Virus

Human Papilloma Virus (HPV) is strongly associated with cervical cancer, particularly the oncogenic genotypes 16 and 18.[320,321] However, there are a number of other genotypes that whilst not as strongly oncogenic, still pose an increased risk.[321,322] HPV testing is now

well-established as being more sensitive at identifying cervical cancer precursors than liquid-based cytology and has been introduced as the primary cervical cancer screening test in a number of countries, including Aotearoa New Zealand.[322–324] However, most identify only HPV 16, 18 or HPV Other (non-16/18 genotypes).

In most HPV-based programmes, a referral for colposcopy is the default for a positive HPV16/18 test given the strong association between these genotypes and cervical cancer. For HPV Other genotypes, infections are often transient and do not result in cervical changes, but distinguishing which will be transient and which may persist and cervical changes/cancer is an area of some uncertainty.[321,322,324] It is known that HPV infections persisting for more than one to two years have a higher risk of cervical cancer, and that persistence is more likely in those over 30 years of age.[321] With colposcopy services often having limited capacity, there is a need to optimise triage protocols to determine who should be referred.[321,324]

Using HPV genotyping stratification has the potential to reduce over-referral and increase the effectiveness of HPV-based cervical screening programmes and this is an area of active research.[321,324] The use of biomarkers for further triaging is also being studied, particularly in the context of increasing HPV 16/18 vaccination coverage.[324,325]

Internationally, there is a focus on triaging for referral and screening intervals.[322,324] Australia was one of the first countries to adopt a national cervical cancer screening programme using HPV testing as the primary screen and where a proportion of vaccinated women have been included.[322] Real-world findings and data following a review of the first two years of the Australian programme have strongly informed adjustments to the programme.[322] This has included reviewing triaging and risk stratification, particularly for HPV Other detected tests.[322] These findings were considered in the introduction of HPV primary screening into the National Cervical Cancer Screening Programme (NCCSP) in Aotearoa New Zealand, which commenced in September 2023.[326]

Colorectal cancer

Colorectal cancer is one of the most common cancers worldwide.[327] Aotearoa New Zealand has one of the highest rates in the world and it is the second highest cause of cancer deaths.[328] Late-stage diagnosis contributes to its relatively high mortality rate and early detection including through screening, is critical to improving outcomes.[327,328]

In many countries including Aotearoa New Zealand, colonoscopy demand is increasing on the background of constrained capacity. The majority of those with a positive screening test referred on for colonoscopy will not have colorectal cancer.[307]

Variables such as sex, body mass index, family history, smoking status, and biomarkers (of which the currently used faecal immunochemical test, or FIT, is one) could be used to stratify risk and modulate the screening frequency or the positivity threshold of the primary

screening test.[307] Identifying appropriate risk factors can be difficult when a number associated with colorectal cancer are related – such as diabetes and weight. Different scenarios would need to be considered and understood – for example, how to manage a low risk with a high FIT result and vice versa.[307]

Currently, there is some evidence that using the FIT with other risk factors may be better at predicting risk than a FIT alone.[307] A large number of multivariate screening models have been developed for colorectal cancer, but most are research-based only, and many have not been externally validated.[307] Whilst the potential to improve benefits and reduce harms for colorectal cancer through risk stratification is recognised, current evidence remains limited including cost effectiveness and applicability to different settings and populations.[307] However, it is an important area for research.

Lung cancer

Lung cancer is the leading cause of cancer-related deaths in Aotearoa New Zealand and a significant contributor to the life expectancy gap between Māori and Non-Māori.[329] The high mortality is in large part due to late-stage diagnosis.[330] However, whilst large randomised controlled trials (RCTs) have demonstrated a reduction in lung cancer mortality using low-dose computed tomography (CT) to screen for lung cancer, associated harms have also been identified, including overdiagnosis, radiation exposure, and false positives.[312]

Initial trials on screening generally considered age and cumulative lifetime smoking exposure ('pack year criteria'). These appeared to provide a sufficiently high 'average' cancer risk for a population of smokers, but did not consider individual risk. However, even for those meeting pack year criteria, most individuals do not develop lung cancer. Assessment of individual risk has the potential to improve benefits and reduce harms at an individual and a population level.[312]

Various models have been developed and have shown improved performance at identifying those smokers at higher risk, but optimal methods are still being determined, including how to apply models in practice.[312] Of particular importance in the Aotearoa New Zealand context is ensuring models are applicable to the Aotearoa New Zealand population, including for Māori, and to ensure existing inequities are not exacerbated. The carcinogenic effects of smoking vary between ethnicities with evidence that African Americans have a higher risk at any given age and pack history, and Hispanic populations having a lower risk, compared with non-Hispanic white populations.[312] The accuracy of risk predictions for different population groups is being assessed in current Aotearoa New Zealand research.

Risk stratification could also be used to determine screening intervals. Current guidelines on the management of nodules identified through low-dose CT screening results in a high proportion of negative CTs.[312] The imaging is a substantial proportion of screening costs

and there is limited capacity for radiologist and medical imaging technologists in many countries, including Aotearoa New Zealand.[312] There are a number of prospective RCTs currently assessing risk stratified approaches to determining screening intervals.[312]

Biomarkers are a further area of research and have the potential to be included in risk stratification models, although current evidence on their clinical utility and cost-effectiveness is limited.[312]

Finally, risk prediction developed for lung cancer screening has the potential to be of benefit in smoking cessation.[312] Personalised smoking interventions using risk stratification developed for lung cancer screening may be of value in communicating and quantifying effects of cessation on subsequent lung cancer risk and life expectancy for an individual.[312] The co-benefits of smoking cessation beyond lung cancer risks are significant.

13.3 Technical Review Process, Questions and Answers

Process

The working group developed a project plan to identify and summarise current knowledge of mammographic breast density, how it is measured and distributed in the population and any association with risk of developing breast cancer. Additionally, the plan aimed to investigate current practices in breast density reporting and guidance for supplemental breast screening for women with dense breasts. A number of questions were raised in order to address the areas of interest and were used as a basis for a literature review. Some additional topics were identified during the review process to provide background information. A Te Whatu Ora Waitematā Librarian supported the literature review team with development of the search strategy and execution of the searches, with the working group members undertaking the assessment of results and determination of included studies. A separate search was conducted for each question, using relevant key search terms, including English language. Searches were conducted in Medline, CINAHL Complete, Google and Google Scholar as at June 2024. The results of each search were reviewed for potentially relevant articles, by title and then abstract. Full text review was then undertaken on this shortlist with further relevant articles identified through review articles and reference lists. Additional key references published after this date were included where they were deemed to be of substantial significance to the report.

Questions and Answers

How much risk does breast density confer relative to other known risk factors for breast cancer?

- Women with higher breast density have an increased risk of developing breast cancer compared to those with low breast density.

- There are two separate risks associated with the measure of dense breasts: a higher incidence of breast cancer development and masking of cancer in mammogram interpretation.
- Studies suggest that the risk can range from 2 to 5-fold, which is comparable to the relative risk of a moderate penetrance genetic mutation. High penetrance breast cancer mutations such as BRCA1/2 have a relative risk of 5 to 12-fold depending on the study.

How is breast density distributed in the population? That is, for whom does this risk apply and to what degree?

- Potentially half of the female population are affected by dense breasts, with 6-10% considered to have extremely dense breasts and 40-45% heterogeneously dense in international studies.
- The distribution of breast density in the Aotearoa New Zealand female population is relatively unknown. One Aotearoa New Zealand based study, published in 2013, demonstrated that wāhine Māori have higher absolute breast density compared to the New Zealand European/Other population.

Can breast density be measured? Are there issues with the measurement itself? What is the current state, with software, with artificial intelligence?

- Breast density is typically evaluated using two-view mammograms and classified according to the American College of Radiology's Breast Imaging-Reporting and Data System (BI-RADS). The BI-RADS atlas provides a density scale including four categories, Category A (almost entirely fatty breasts), Category B (scattered areas of fibroglandular density), Category C (heterogeneously dense) to Category D (extremely dense breasts).
- BI-RADS reported distribution in the general female population is A – 10% fatty, B – 40% scattered, C – 40% heterogeneous and D – 10% extremely dense.
- Breast composition is defined by mammographic visually estimated content of fibroglandular-density tissue within the breasts and categorised accordingly. Visual assessment can be highly subjective and varies between observers (inter-observer variability) as well as in the same observer over time (intra-observer variability)
- Artificial intelligence (AI) was developed to provide a more objective and standardised measurement. Algorithms consisting of three broad approaches, physics based, machine learning based or deep learning based have been utilised in tools to measure breast density.
- Volpara, an Aotearoa New Zealand based company provides a well validated physics-based tool (with MedSafe approval) for automated breast density reporting. The output is either through Digital Imaging and Communications in Medicine (DICOM) structured

reports or DICOM secondary capture images and integrates into the Picture Archive Communication System (PACS) reading workflow. Density grade, fibroglandular tissue volume, breast volume, and volumetric breast density percentage for left and right breasts are all reported.

What happens currently with breast screening in Aotearoa New Zealand (BreastScreen Aotearoa and privately)? What is happening in other countries?

- In Aotearoa New Zealand the publicly funded breast screening programme (BreastScreen Aotearoa (BSA)) does not measure or report on breast density. Approximately 69% of eligible women aged 45 to 69 undergo breast screening every 2 years and there is significant inequity in coverage by ethnicity, with lower coverage rates achieved by BSA for Māori women.
- Breast density reporting is available to women in Aotearoa New Zealand who have health insurance or pay for screening through private providers, with mixed advice being given on supplemental screening for women with dense breasts.
- In Australia, New South Wales, Western and South Australia report breast density in their screening programmes. Western Australia and New South Wales do not offer supplemental screening within their screening programme but direct women to discuss with their GP to receive further advice on their breast cancer risk and supplemental screening options. Breast density reporting has been mandated in the USA, is reported in most Canadian territories and is recommended by the European Society of Breast Imaging (EUOSBI), with at least 9 European countries incorporating reporting. The United Kingdom and Ireland do not report breast density.

Would routinely returning breast density results lead to benefit (morbidity, mortality, quality of life, choice, information)?

- The outcome benefits of breast density reporting are yet to be fully evidenced. This is due mainly to a lack of clinical trials having completed mortality follow up.
- Supplemental screening for women with dense breasts has been shown to increase cancer detection rates, to detect cancers earlier and to decrease the rate of interval cancers.
- Providing beast density information supports women’s autonomy to make informed decisions about their care.
- Qualitative studies of breast screening programme participants have reported that women informed about breast density want to know their breast density, agreeing it would make them feel more informed to make decisions about their health. In most cases, this view remained when made aware of uncertainty about what, if any, additional tests should be done for women with dense breasts.

- Many women with dense breasts stated that they had or would intend to have additional surveillance or more frequent mammograms.
- However, without providing equitable access to any additional care (e.g. supplemental screening), advising women of their breast density risks exacerbating existing breast cancer inequities.

Are there risk stratification/triage approaches based on a high-density result, such as more intensive screening or alternate modalities?

- Methods for breast cancer risk stratification vary, with a number of tools available utilising different criteria, of which 3 currently include breast density.
- Supplemental breast screening has been recommended for women deemed to be at high risk of developing breast cancer. Screening options including MRI, ultrasound and CEM have been shown to increase the detection of cancer compared to standard mammography but all are associated with varying risks and benefits.
    - MRI has the greatest sensitivity for cancer detection but with an increased false positive rate and is a costly procedure.
    - Ultrasound is not as sensitive as MRI and has a similar false positive rate, however, it is a less invasive and less costly procedure.
    - CEM is nearly as effective as MRI for cancer detection, with less false positives and is a simpler, lower cost method, however, is not routinely available.
- The following organisations recommend supplemental screening for women with dense breasts; The European Society of Breast Imaging (EUSOBI), The American College of Radiology (ACR), The Gynaecological Oncology Working Group (AGO), The National Comprehensive Cancer Network (NCCN), The American Cancer Society (ACS), The German Guideline Program in Oncology, The Gynaecological Oncology Working Group (AGO), The Brazilian College of Radiology and Diagnostic Imaging (CBR), Brazilian Breast Disease Society (SBM), The Brazilian Federation of Gynaecological and Obstetrical Associations (Febrasgo) and the China Anti-Cancer Association.

What information on breast density is available for women/consumers?

- Online information is not generally presented in a manner that is easy to understand or act upon and there is no consistent pattern of content.
- The majority of online information is based on what breast density is, how it is measured and what dense breasts means.
- Only a few websites directly address benefits and harms of measuring and reporting breast density and these were mainly focused on the use of supplemental screening.

- The most common recommendation was for women to talk with their doctor to discuss what breast density means for them, their individual risk and supplemental screening options.

Are there harms or other ethical issues to consider for women such as anxiety or overscreening?

- There is the potential for anxiety and confusion regarding notification of breast density, understanding breast density advice, exposure to and cost of further investigations.
- Incorporation of supplemental screening for women with dense breasts may increase overdiagnosis and false positive findings.
- Ethical issues to consider include equitable care, patient autonomy, healthcare professional trust, duty of care and uncertainties relating to measurement and clinical management pathways for women with dense breasts.
- Further research is required to determine health benefits, cost effectiveness of supplemental screening options, patient perspectives and maintenance of equity in service provision.

What are the programme, health professional and consumer perspectives on the measurement of breast density within screening programmes?

- There are mixed views among healthcare professional on the merits of breast density reporting, with radiologists appearing to be more hesitant about it compared with GPs.
- Healthcare professionals highlight the need for consensus statements and national guidelines on breast density reporting, and clarity on recommendations (or otherwise) regarding supplemental imaging of dense breasts.
- Measuring and reporting breast density in the absence of consistent guidelines for follow-up can lead to inconsistent management as well as anxiety and confusion for the provider and patient.
- Healthcare professionals emphasised the need for education and to contextualise breast density information with other risk factors for breast cancer.
- Most breast screening participants wanted to know their breast density, stating it would make them feel more informed to make decisions about their health. In most cases, this sentiment held when they were informed that there was uncertainty about what, if any, additional tests should be done for women with dense breasts.
- Many women with dense breasts stated that they had or would intend to have additional testing or more frequent mammograms. However, studies found reduced uptake of additional testing for women of ethnic minorities and lower socio-economic status.

- Reporting breast density also created anxiety and confusion for a proportion of women. Women stated the need for clear information about the implications of breast density and many expressed a preference for discussing the result with a healthcare professional who could contextualise the results and address any confusion and anxiety.
- There is no published evidence of the opinions of breast screening participants in Aotearoa New Zealand on reporting breast density, however, Aotearoa New Zealand breast cancer organisations Breast Cancer Foundation New Zealand and Breast Cancer Aotearoa Coalition are in favour of breast density being reported by BreastScreen Aotearoa.
- International evidence suggests significant resource implications for the health system in terms of additional imaging demand and participants' desire for discussion of results with a healthcare professional.

If there are benefits, what would it take to implement breast density measurement and management in BreastScreen Aoteaora (including costs, programme changes, staffing, cost benefit/effectiveness, research)?

- Breast density reporting could be facilitated automatically through a software provider at a cost. There would also be wider costs associated with reporting e.g. software licenses, workforce time to support participation.
- Alternatively, breast density could be manually measured by radiologists at the additional cost of extensive auditing of assessment and training to ensure consistency of reporting.
- BreastScreen Aotearoa is rolling out a new information communication infrastructure which offers an opportunity to consider AI in this context.
- BreastScreen Aotearoa workforce is currently operating at capacity and feedback from BreastCare nurses and Medical Imaging Technologists (mammographers) is that there is limited capacity at current staffing levels to talk through breast density results with women.
- BreastScreen Aotearoa does not have the funding or capacity within the programme to undertake further ultrasound assessments.
- Hospital and Specialist Services have reported that capacity to fulfil supplementary ultrasound or MRI within the wider health system is limited.
- A more detailed assessment of whole system capacity issues is required.

13.4 National Health Committee (NHC) screening criteria assessment

Table 8: NHC Screening Criteria Assessment

Screening criteria		Assessment	Comment
	Breast density reporting	**Supplemental screening for breast density**	
The condition is suitable for screening	Met	Met	Breast density increases the risk of breast cancer and can also reduce the detection of breast cancers on mammograms (see page **Error! Bookmark not defined.**).
There is a suitable test	Met	Met	There are simple, safe, reliable tests for breast density that are validated, sensitive and specific (see page 24). Density grading using currently available software can be correlated with the BI-RADS classification system.
There is an effective and accessible treatment or intervention for the condition	Met for breast cancer	Met for breast cancer	Evidence shows that early treatment for breast cancer improves outcomes.
There is high-quality evidence that a screening programme is effective in reducing death and illness	Met for the programme, inconclusive for breast density	Met for the programme, inconclusive for supplemental screening	There is high quality evidence that population-based breast cancer screening programmes reduce morbidity and mortality from breast cancer. There is no evidence as yet that measuring breast density or supplemental screening reduces mortality for

Screening criteria		Assessment	Comment
	Breast density reporting	**Supplemental screening for breast density**	
			women with dense breasts (see page 38)
The potential benefit of the test should outweigh potential harm	Inconclusive	Inconclusive	The benefit of reporting breast density to women is contingent upon meeting patient needs following receipt of this information e.g. having someone to discuss results with, health literacy needs being met, able to access to additional screening / care / management as appropriate (see page 38). There is evidence that supplemental screening for dense breasts improves cancer detection and outcomes (see page 38).
The health sector should be capable of supporting diagnosis, follow-up and programme evaluation	Not met	Not met	Currently BreastScreen Aotearoa does not have the funding or capacity within the programme to implement supplementary screening. Hospital and Specialist Services have informed the NSU that if supplementary screening is recommended to women who have dense breasts, capacity to fulfil this within the wider health system is also limited. There are also significant capacity constraints currently for both

Screening criteria		Assessment	Comment
	Breast density reporting	Supplemental screening for breast density	
			MRI and Ultrasound services – with waiting times generally significantly longer than clinically indicated.
There is consideration of social and ethical issues	Not met	Not met	Breast density differs by ethnicity, with one study finding Māori have higher absolute volumetric density than New Zealand Europeans. Combined with the higher incidence of breast cancer and higher mortality for wāhine Māori, it is critical that adding breast density reporting and other changes (such as supplementary screening) to the BreastScreen Aotearoa programme does not further entrench or increase inequities in breast cancer outcomes for Māori. There are also inequities in cancer outcomes by other sociodemographic factors such as rurality and socioeconomic deprivation (NZDep) which need to be considered and addressed. Consideration should also be given to the opportunity costs of including any breast density-related changes to the programme.

Screening criteria		Assessment	Comment
	Breast density reporting	**Supplemental screening for breast density**	
			Patient views should also be sought and considered for any proposed changes to the BreastScreen Aotearoa programme.
There is consideration of cost-benefit issues	Not met	Not met	Cost to the programme per screen by a provider has been sought and supplied. The full cost will include additional services that could be required e.g. explanation of results and further discussion with a health worker, supplementary screening etc.

13.5 Mammogram Breast Density Related Screening Recommendations

Table 9: Breast density related screening guidelines/recommendations/position statements

Professional Organisation	Year	Measure BD	SS	Recommendation and relevant comments
European Commission Initiative on Breast Cancer Guideline Development Group GDG[232]	2020		No	Tailored screening for MBD – Yes DBT for women with high MBD. Guiding supplemental screening – No
European Society of Breast Imaging (EUSOBI)[224]	2022	Yes	Yes	MBD notification “Should be informed on the diagnostic and prognostic implications of having dense breasts”.

Professional Organisation	Year	Measure BD	SS	Recommendation and relevant comments
				Guiding supplemental screening – Yes "SS with MRI at least every 4 years, preferably every 2–3 years for women with extremely dense breasts aged 50–70. If MRI screening is unavailable, US in combination with DM may be used".
The German Guideline Program in Oncology (German Cancer Society, German Cancer Aid, Association of Scientific Medical Societies (AWMF))[233]	2021		Yes	Guiding supplemental screening – Yes SS with "US appears to be the most suitable method". Improved sensitivity but lack of long-term evidence that it reduces mortality and "associated with a higher rate of biopsies than the national screening program". Use of tomosynthesis can increase sensitivity and "should be considered for testing in a quality assured programme".
The German Gynaecological Oncology Working Group (AGO)[234]	2020		Yes	Guiding supplemental screening – Yes Breast US for heterogeneously dense, extremely dense mammograms. MRI if screening mammogram is negative and breast composition extremely dense* 50–75 years old.
The Royal College of Radiologists (United Kingdom)[235]	2019	High-risk	No	Guiding supplemental screening – No Adjunctive US screening is not routinely recommended.

Professional Organisation	Year	Measure BD	SS	Recommendation and relevant comments
The Royal Australian and New Zealand College of Radiologists[219]	2018	Yes	No	MBD reporting Formal report not issued in screening programmes in Australia or Aotearoa New Zealand.
The Brazilian College of Radiology and Diagnostic Imaging (CBR), Brazilian Breast Disease Society (SBM), and Brazilian Federation of Gynecological and Obstetrical Associations (Febrasgo)[236]	2017		Yes	Guiding supplemental screening – Yes Complementary US should be considered
Alberta Breast Cancer Screening Clinical Practice Guideline[237]	2022		Yes	Guiding supplemental screening – Yes Annual mammography and consider annual breast US and consider annual clinical breast exam
China Anti-Cancer Association[238]	2019		Yes	Guiding supplemental screening – Yes Breast US.
The Japanese Breast Cancer Society[239]	2018	Yes	No	MBD assessment – Yes MBD notification – No Guiding supplemental screening – No
American College of Radiology[240]	2021		Yes	Guiding supplemental screening – Yes DBT screening usually appropriate May be appropriate for average risk females with dense breasts; US breast, Mammography with IV contrast, Abbreviated/MRI breast with and without IV contrast

Professional Organisation	Year	Measure BD	SS	Recommendation and relevant comments
American College of Obstetricians and Gynecologists[241]	2020	Yes	No	MBD notification Guiding supplemental screening – No
American Cancer Society[137]	2007		No	Guiding supplemental screening "Insufficient evidence to recommend for or against breast MRI screening for women with heterogeneously or extremely dense breasts."
The National Comprehensive Cancer Network[242]	2024		Yes	Guiding supplemental screening For individuals ≥40 years of age with heterogeneous or extremely dense breasts, consideration should be made for supplemental screening.
The Society of Breast Imaging[243]	2010		Yes	Guiding supplemental screening – Yes US may be considered for women with dense breasts
The United States Preventive Services Task Force (USPTSF)[244]	2016		No	Guiding supplemental screening Insufficient evidence to assess the balance of benefits and harms of SS using breast US, MRI, DBT, or other methods
The American Academy of Family Physicians[245]	2021		No	Supports USPSTF recommendation

MBD = Mammographic breast density, SS = Supplemental screening, IV= Intravenous DM = Digital Mammography, US = Ultrasound, DBT = Digital Breast Tomosynthesis, MRI = Magnetic Resonance Imaging

Adapted from: O'Driscoll J, et al. A scoping review of programme specific mammographic breast density related guidelines and practices within breast screening programmes. Eur J Radiol Open. 2023 Aug 2;11:100510.

13.6 Current risk–based breast cancer screening randomised control trials

The following tables were sourced from: The ROSA Project: Roadmap for Optimising Screening in Australia – Breast. Chapter 5: Implementation (Abridged). 20 March 2023, abridged 1 May 2024. Produced by the Daffodil Centre on behalf of Cancer Council Australia.

Table 10: Summary of trials comparing risk-based screening with standard non-risk-based screening

Trial name and ID	**MyPeBS – Randomized, Comparison of Risk-Stratified versus Standard Breast Cancer Screening In European Women Aged 40-70 NCT03672331**		
Population	**Intervention**	**Comparator**	**Outcomes**
Women aged 40-70 years affiliated to a social security or national healthcare system With no prior DCIS or breast cancer, atypical breast lesion, lobular carcinoma in situ or chest wall irradiation or known or suspected very high-risk germline mutation France, Italy, UK, Belgium and Israel	Personalised risk-based screening protocol for 4 years, according to estimated 5-year risk of breast cancer. Risk determined using algorithm incorporating BCSC score and Tyrer-Cuzick score for women with more than one first degree relative with breast or ovarian cancer. Both scores will be modified to incorporate genotyping results and will be adjusted for country-specific breast cancer incidence. Risk stratified screening protocols are as follows: Low risk (<1% 5-year risk): Quadrennial	Mammogram with or without supplemental imaging according to guidelines in each participating country for 4 years: Belgium (Brussels, Leuven): Biennial mammogram +/- tomosynthesis for women aged 50-69 years Italy (4-6 regions): Biennial mammogram for all women aged 50-69 years, and up to 74 years in some regions. Annual mammogram for women aged 45-49 in some regions UK (Cambridge, Manchester, Leeds):	Primary outcome 4 years follow-up (end of intervention) Stage 2 or higher breast cancer incidence – non-inferiority Secondary outcomes 4 years follow-up (end of intervention) Stage 2 or higher breast cancer incidence – superiority False positive rate Benign biopsy rate Anxiety Quality of life Cost-effectiveness Stage specific breast cancer and DCIS incidence Overdiagnosis rate Interval cancer rate

Trial name and ID	MyPeBS – Randomized, Comparison of Risk-Stratified versus Standard Breast Cancer Screening In European Women Aged 40-70 NCT03672331		
	mammogram for all women (i.e at study entry and end) Average risk (1-<1.67% 5-year risk): Biennial mammogram for all women + ultrasound or ABUS for women with “high” breast density High-risk (1.67-<6% 5-year risk): Annual mammogram for all women + ultrasound or ABUS for women with “high” breast density Very high-risk (≥6% 5-year risk): Annual mammogram + MRI for all women Supplemental tomosynthesis and/or ultrasound will be performed in this arm according to standard screening guidelines in each participating country (i.e. per comparator)	Triennial mammogram for women aged 50-73 years Israel (national): Biennial mammogram for women aged 50-74 years +/- tomosynthesis +/- ultrasound per radiologist France (national): Biennial mammogram for women aged 50-74 years + ultrasound in all women with dense breasts	10 years and 15 years follow-up Cumulative incidence of all breast cancer and stage 2 or higher breast cancer Breast cancer-specific survival
Women aged 40-74 years With no prior DCIS or breast cancer USA	Personalised risk-based screening protocol for 5 years, according to estimated 5-year risk of breast cancer.	Annual mammogram	Primary outcome 5 years follow-up Proportion of cancers stage IIB or higher – non-inferiority Biopsy rate Secondary outcomes

Trial name and ID	MyPeBS – Randomized, Comparison of Risk-Stratified versus Standard Breast Cancer Screening In European Women Aged 40-70 NCT03672331		
	Risk determined using the BCSC model, genetic testing for rare high/moderate-penetrance mutations in nine genes and polygenic risk score for 96 lower-risk common genetic variants with known association to breast cancer. Risk stratified screening protocols are as follows: Lowest risk (aged 40-49 with <1.3% 5-year risk): No screening until age 50 Average risk (aged 50-74; or aged 40-49 with ≥1.3% 5-year risk): Biennial mammogram (if individual does not meet elevated or highest risk criteria) Elevated risk (aged 40-49 with BI-RADS 4, or ≥0.75% 5-year risk of ER-breast cancer based on age and ethnicity; or women in top 2.5th percentile of risk by 1-year age category; or ATM, PALB2 or CHEK2 mutation carrier		5 years follow-up Stage IIB or higher breast cancer rate Interval cancer rate Systemic therapy rate Mammogram recall rate Breast biopsy rate DCIS rate Chemoprevention uptake rate Participant preference – risk- based vs annual screening (in self-assigned cohort) Participant adherence to assigned screening schedule Breast cancer anxiety (PROMIS anxiety scale) Decisional regret (Decision Regret Scale) Ultra-low risk cancer rate

Trial name and ID	MyPeBS – Randomized, Comparison of Risk-Stratified versus Standard Breast Cancer Screening In European Women Aged 40-70 NCT03672331		
	without a positive family history* of breast cancer): Annual mammogram (if individual does not meet highest risk criteria) Highest risk (BRCA1/2, TP53, PTEN, STK11, CDH1 mutation carrier; or ATM, PALB2, or CHEK2 mutation carrier with positive family history of breast cancer; or ≥ 6% 5-year risk; or had mantle radiation when aged 10-30): Annual mammogram + MRI *Family history: first degree relative with breast cancer, two second-degree relatives with breast cancer, or one second- degree relative diagnosed prior to age 45		
Premenopausal women aged 44-45 years resident in screening centre catchment area invited to attend	Risk-based screening for women aged 45-50 years according to breast density (BI-RADS classification).	Annual invitation to mammography for women aged 45-49 years After the age of 50 years, all women will continue to be	By arm and breast density group: Primary outcomes 3 years and 6 years follow-up

Trial name and ID	MyPeBS – Randomized, Comparison of Risk-Stratified versus Standard Breast Cancer Screening In European Women Aged 40-70 NCT03672331		
for mammographic screening With no prior DCIS or breast cancer, family not at high-risk for breast cancer and no diagnosis of other cancer in last 5 years Italy	Risk stratified screening protocols are as follows: Low risk (low breast density; BI-RADS 1-2 on baseline mammogram): Biennial mammogram until aged > 50 years High-risk (high breast density; BI-RADS 3-4 on baseline mammogram): Annual mammogram After the age of 50 years, all women will continue to be screened in the usual service screening programme	screened in the usual service screening programme (In Italy biennial mammogram for all women aged 50-69 years, and up to 74 years in some regions. Annual mammogram for women aged 45-49 in some regions)	Cumulative incidence of interval cancer – non-inferiority Cumulative incidence of T2+/node- positive breast cancer – non-inferiority Secondary outcomes 3 years and 6 years follow-up False positive rates Cumulative incidence of breast cancer 1, 2, 3 ,4, 5 years and 6 years follow-up Mammography screening attendance
Women aged 45-49 years resident in four locations in Italy With no prior DCIS or breast cancer, no familial risk for breast cancer and no concurrent participation in another clinical trial on breast	Biennial tomosynthesis OR Risk-based screening for women aged 45-49 years according to breast density (BI-RADS classification): Low risk (breast density; BI-RADS category A-C): Biennial tomosynthesis until aged 50 years High-risk (breast density; BI-RADS	Unclear – Annual tomosynthesis? (aim is to compare screening intervals not screening modalities)	Primary outcome 6 years follow-up Cumulative incidence of cancers stage II or higher – non- inferiority Secondary outcomes 6 years follow-up Participation rate within 3 months of invitation Proportion of women allocated biennial screen who have a screen performed prior to next 2- year screen

Trial name and ID	MyPeBS – Randomized, Comparison of Risk-Stratified versus Standard Breast Cancer Screening In European Women Aged 40-70 NCT03672331		
cancer screening	category D): Annual tomosynthesis		Breast cancer detection rate Overall recall rate Recall rate involving an invasive procedure Interval breast cancer rate Cumulative breast cancer incidence Resource expenditure Prevalence of dense breast in the target population

ABUS = automated breast ultrasound; BCSC = Breast Cancer Surveillance Consortium; BI-RADS = Breast Imaging and Reporting Data; DCIS = ductal carcinoma in-situ; HRT = hormone replacement therapy; MRI = magnetic resonance imaging; NA = not applicable; NHS-BSP = National Health Service – Breast Screen Programme

Table 11: Trials comparing different or additional screening modalities with standard screening for higher risk groups

Trial name and ID	DENSE – Breast Cancer Screening With MRI in Women Aged 50-75 Years With Extremely Dense Breast Tissue NCT01315015		
Population	**Intervention**	**Comparator**	**Outcomes**
Asymptomatic women aged 50-75 years participating in population-based screening program With extremely dense breasts (Volpara grade 4/D) and a	Biennial MRI + mammogram for 4 years (3 screening rounds)	Biennial mammogram for 4 years (3 screening rounds)	Primary outcome 6 years follow-up Incidence of interval cancer Secondary outcomes 6 years follow-up Tumour size, stage, grade, histology and molecular subtype

Trial name and ID	DENSE – Breast Cancer Screening With MRI in Women Aged 50-75 Years With Extremely Dense Breast Tissue NCT01315015		
negative mammogram Netherlands			Mortality rate (MISCAN program) Cost-effectiveness (MISCAN program) Quality of life (MRI group) 4 years follow-up MRI screen-detected cancer MRI referral rate PPV (MRI group) Number of biopsies per MRI referral
Women aged 50-70 years undergoing triennial population-based screening (NHS-BSP) With dense breasts (BI-RADS C with high chance of masking or D) on baseline (current) mammogram (negative or positive) With no known BRCA mutation or < 50% risk of being a BRCA carrier U.K.	Mammogram + abbreviated-MRI at baseline and 18 months; mammogram at 3 years or Mammogram + ABUS at baseline and 18 months; mammogram at 3 years or Mammogram + contrast-enhanced spectral mammogram at baseline; contrast-enhanced spectral mammogram only at 18 months; mammogram at 3 years	Triennial mammogram	Primary outcome 3 years follow-up Cancer detection rates Secondary outcomes 3.5 years follow-up Stage II or higher cancer incidence Cancer detection rate Interval cancer rate Recall rate Sensitivity of supplemental imaging Specificity of supplemental imaging 0.5 year and 1.75 years follow-up Cancer detection rate Recall rate Sensitivity of supplemental imaging Specificity of supplemental imaging 1 year follow-up

Trial name and ID	DENSE – Breast Cancer Screening With MRI in Women Aged 50-75 Years With Extremely Dense Breast Tissue NCT01315015		
			Cost-effectiveness of each modality

ABUS = automated breast ultrasound; BCSC = Breast Cancer Surveillance Consortium; BI-RADS = Breast Imaging and Reporting Data; DCIS = ductal carcinoma in-situ; HRT = hormone replacement therapy; MRI = magnetic resonance imaging; NA = not applicable; NHS-BSP = National Health Service – Breast Screen Programme

13.7 Project ROSA

The Australian based ROSA project produced a number of detailed technical reports on risk-based breast cancer screening and published a set of evidence-based recommendations (see below) alongside a roadmap summarised into 5 pillars (see Figure 11) to guide considerations over the subsequent 4-5 years.

Project ROSA Recommendations

Policy and guideline reviews – That national BreastScreen Australia guidelines are developed including current policies and practices in relation to women with different risk factors, including women presenting with known high-risk mutations. That current management outside BreastScreen Australia of women assessed at moderately higher breast cancer risk be reviewed, aiming for clear and consistent guidelines and management pathways.

Clinical studies to support trial design - That a well-validated, automated breast density assessment tool is evaluated on a large scale in a BreastScreen Australia setting, reporting on outcomes in the setting such as cancer diagnosis rates, interval cancer rates and false positive screening rates for defined breast density groups. That well-validated breast cancer risk assessment tools are evaluated in BreastScreen Australia settings to continue to build the evidence base towards risk-based breast cancer screening. That technologies for consideration in this context include digital breast tomosynthesis, ultrasound, MRI and contrast-enhanced mammography as primary or supplemental screening tools in some risk-stratified screening group/s.

Trial participation - That evidence on risk-based breast cancer screening is continually reviewed in relation to risk-based screening protocols.

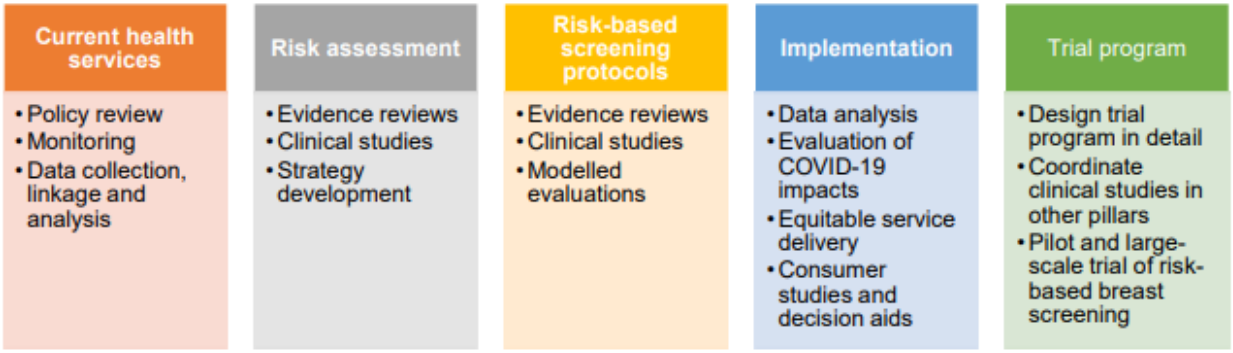
Enhanced data collection and reporting - That BreastScreen Australia develop a framework for data collection and analysis to inform policy and practice for optimal risk-based breast screening.

Data linkage and evaluation of linked data - That BreastScreen data and other health records are linked and analysed to help evaluate ad hoc risk-based breast cancer screening occurring in asymptomatic women outside BreastScreen.

Targeted evidence reviews - That ongoing evidence review includes consideration of factors such as participant/patient history, validation and improvement of risk tools, genetic tests, breast density and evolving technologies. That ongoing evidence review includes estimated group-level benefits and harms of risk-based breast screening technologies. That any implemented approaches to risk-based breast screening technologies be regularly reviewed to ensure optimal approaches to policy and practice are being applied.

Research to address priority evidence gaps - That learnings from the management of COVID-19 and its impact on screening participation, service responses and outcomes are considered in relation to prioritised and stratified approaches to risk-based breast cancer screening.

Figure 11: Project ROSA Roadmap five pillars



Recommended actions summarised under the 5 pillars

Current health services

- That a framework for data collection and analysis is established to inform potential policy and practice options towards risk-based breast cancer screening.
- That national BreastScreen Australia data on participants aged 40-49 is utilised to inform longterm considerations for targeted approaches to risk-based breast cancer screening.
- That BreastScreen data and data on ad hoc breast cancer screening (where feasible) are linked and analysed in relation to hospital admissions, Medicare, PBS and other datasets (including, potentially, through use of deidentified My Health Record data).
- That linked data is used to evaluate ad hoc risk-based breast cancer screening occurring in asymptomatic women outside BreastScreen.

- That BreastScreen Australia guidelines are developed including current policies and practices in relation to women with different risk factors, as work continues towards risk-based breast cancer screening.

Risk assessment

- That well-validated breast cancer risk assessment tools are evaluated in BreastScreen Australia settings to continue to build the evidence base towards risk-based breast cancer screening.
- That ongoing evidence review includes a focus on optimal analysis of factors such as participant/patient history, genetic tests, breast density and evolving technologies.
- That a well-validated automated breast density assessment tool is evaluated on a large scale in a BreastScreen Australia setting, reporting on outcomes, the setting such as cancer diagnosis rates, interval cancer rates and false positive screening rates for defined breast density groups.
- That evidence on the effectiveness of breast density tools be continually collected towards developing policy and practice for risk-based breast cancer screening.

Risk-based screening protocols

- That priorities for future targeted research include a focus on the expected benefits and risks of potentially important technologies in relation to risk-based breast cancer screening.
- That technologies for consideration in this context include digital breast tomosynthesis, ultrasound, magnetic resonance imaging and contrast-enhanced mammography as primary or supplemental screening tools in some risk-stratified screening group/s.
- That well-validated breast imaging techniques for improved cancer staging at diagnosis are evaluated in a BreastScreen Australia setting.
- That evidence on risk-based breast cancer screening is continually reviewed in relation to riskbased screening protocols.
- That any evolving approaches to introducing risk-based breast cancer screening are supported in parallel by coordinated evidence review, including modelling studies and analysis of other trials and pilot studies.
- That modelled evaluations of risk-based breast cancer screening protocols in the Australian setting be used to help identify priority screening protocols to consider for real-world evaluation.

Evidence-based implementation

- That BreastScreen Australia reporting for priority populations (e.g., Indigenous, rural/remote, culturally and linguistically diverse) is enhanced to help ensure any

moves towards risk-based breast cancer screening do not widen gaps in outcomes between population groups.

- That learnings from the management of COVID-19 and its impact on screening participation, service responses and outcomes are considered in relation to prioritised and stratified approaches to risk-based breast cancer screening.
- That steps towards risk-based breast cancer screening include increased engagement between policy, program and research leads and consumers and other key stakeholder groups, and ongoing exchange of clear, evidence-based information.

Trial Programme

- Design and implement of an Australian trial, drawing on clinical studies and other ROSA project recommendations to support it.

Te Kāwanatanga o Aotearoa
New Zealand Government

Health New Zealand
Te Whatu Ora