Breast Density Submission

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BREAST CANCER AOTERAROA COALITION
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Executive Summary

The Breast Cancer Aotearoa Coalition (BCAC) represents over 30 breast cancer charities and groups across Aotearoa, as well as individual members. Our purposes are to support, inform and represent those diagnosed with breast cancer in Aotearoa from an evidence basis.

In January 2023 BCAC provided a comprehensive response to Manatū Hauora's first and second Precision Health request for submissions [1, 2]. Within those submissions we highlighted the need to introduce policy relating to the measurement and reporting of breast density. The DENSE Trial evidence has demonstrated the benefits of doing so for earlier diagnosis and reduction of interval cancers, although more time is needed to demonstrate mortality benefit [3]. BCAC members Fay Sowerby and Libby Burgess also responded to the recent Breast Screen Aotearoa (BSA) Review indicating opportunities available from reporting and measuring breast density to AI were currently being lost. Globally there has been a significant shift in thinking relating to breast density measurement and reporting, with growing acceptance of the overwhelming benefits and, in some instances, the benefits of supplementary screening.

In February 2020, the Society of Breast Imaging (SBI) and American College of Radiology (ACR) updated guidelines [4], assigning a special status and approach for African American women and other women at higher-than-average risk for breast cancer, in recognition of their higher risk status. In March 2022 the recommendations of the European Society of Breast Imaging (EUSOBI) (Appendix 1) were published following results from the DENSE and EA1411 ECOG-ACRIN trials [3, 5]. These determined that women should be informed of their breast density and the diagnostic and prognostic implications of having dense breasts. Further, that supplementary screening should be offered, preferably with full or abbreviated MRI. In a further step forward, the US FDA's guidelines requiring breast density measurement and reporting were published in June 2023 with implementation in 2024 [6]. In unison NCCN also updated its guidelines in 2023 lowering the screening age to 40 and incorporating breast density and flexible surveillance recommendations (Appendix 2). Canada has also made a move to introduce the measurement and reporting of breast density across seven territories, soon to be extended to 10 [7]. BreastScreen South Australia [8] has now joined Western Australia [9] in measuring and reporting breast density. BreastScreen SA Clinical Director, Associate Professor Michelle Reintals, acknowledges that higher breast density has been linked to an increased risk of breast cancer and can reduce the visibility of breast cancers on a mammogram. "While it is common and normal to have high breast density, this knowledge is important as it can inform decisions around breast care and increase breast awareness." [10] Queensland has also introduced a randomised trial on density indicating a move towards acceptance of the evidence as well as the community's demand for a response [11].

Concurrently, through improvements in imaging and AI (artificial intelligence and deep learning) based risk models, studies have shown that high breast density, more complex tissue patterns, high glandular volume and marked background parenchymal enhancement (BPE) on MRI are linked to increased lifetime risk of breast cancer. Extensive retrospective global research has led to prospective trials now reporting the benefits of AI to improve breast screening precision (being demanded by women and providers alike), significant reduction in radiologist resource (timely given a global shortage) and are now demonstrating AI alongside a single image reader is non inferior to screening involving two readers, with no increase in call backs [12, 13].

These trials support women's right to breast density information to help them make well-informed decisions regarding surveillance and to reduce their risk of developing, false negative, interval, high grade and late-stage breast cancer leading potentially to advanced disease and higher morbidity [3].

With the implementation of BSA's new ICT system by mid-2024, we as consumer advocates wish to see BSA include the capacity to measure, record and report density in the new system with timely introduction. We encourage retrospective and observational studies leading to better understanding of modality options through modelling e.g., highest risk individuals accessing MRI, those at intermediate risk Contrast Enhanced Mammography and or ultrasound and those at average risk mammography (Appendix 2).

We want to see policy changed so that we may move from a population-based model to one in which women are also informed of an important element of breast cancer risk to participate in shared decision-making regarding surveillance and screening modalities that will lead to earlier detection of breast cancers and better patient outcomes. This will also better inform individuals and their whānau regarding potential benefits and harms, including those who currently do not see a personal benefit from breast screening.

Along with other elements of precision health, this will contribute to ongoing development and improvements across our health system. We see benefit from research and simulation modelling leading to intervention studies, and retrospective and prospective trials to better inform policy for our unique population. Good policy will help to translate trial and research findings into timely benefits for patients with consequent efficiencies across the system [1,2].

Breast Screen Aotearoa's Request for Submissions

On 3 August 2023 Adam Stewart, Clinical Director BreastScreen Aotearoa (BSA), requested submissions from Breast Cancer Aotearoa Coalition, Breast Cancer Foundation New Zealand and Nikki Robinson Slade of Aotearoa NZ Breast Cancer Community (ANZBCC) regarding Breast Density.

It was noted that "broadly speaking increased breast density is a well-validated independent risk factor for breast cancer and represents a reporting challenge for detecting 'mammographically occult' breast cancers in dense breasts by virtue of the imaging modality itself."

BSA highlighted the following issues to be covered (not an exhaustive list):

1. Evidence-based benefits of measuring reporting breast density (e.g., BIRADS classification)
2. International Best Practice and International Precedents
3. Role of AI (artificial intelligence), accuracy of AI algorithms
4. Māori health equity / Te Tiriti obligations
5. Potential harms of over-reporting, harms of reporting breast density (i.e., the "worried well")
6. Research

BCAC provides a summary of global and local research in this submission.

Previous BCAC submissions on breast density

BCAC has been advocating since 2012 for measurement and reporting of breast density alongside other issues relating to earlier diagnosis, including risk assessment, access to a range of services including provision of these closer to home, extending the screening age, management of those at higher risk, a move towards personalised screening, while bringing a focus to poorer outcomes for Māori and Pasifika patients. Read our submissions on a range of topics [14]. We have raised the issue

of breast density as an issue of concern through formal submissions, papers, at meetings and in social media, magazines and newspaper articles. Submissions include the below:
December 2016, BCAC met with the **Minister of Health Johnathan Coleman** and presented a briefing which made a case for increased medicines funding and outlined other areas of concern. We clearly highlighted breast density as a risk and tumour masking factor and asked that a working group be established to address management of this risk. Read our briefing here.
July 2018, BCAC met with the **Associate Minister of Health Hon. Julie Anne Genter**, Labour's Health and Wellbeing Caucus member Hon. Louisa Wall and National's Health spokesperson Hon. Michael Woodhouse. The two key issues highlighted by BCAC in the talks were the need to improve access to medicines and the need to address inequities for Māori and Pasifika women in breast cancer screening and treatment. We highlighted breast density as a risk factor and the need for risk-stratified screening. Read our briefing here.
May 2019 BCAC made a submission to the **Health and Disability Review**. We stressed the need to introduce an objective risk assessment tool such as BOADICEA which recognises a broader range of breast cancer risk factors including breast density to identify differing levels of risk. Read our submission here.
2019: BCAC and Breast Cancer Cure made a **joint submission** in response to the proposed **Cancer Action Plan 2019-2029**, again highlighting the need to measure and report breast density. Read our submission here.
2020: Fay Sowerby, BCAC Secretary, wrote two papers discussing breast screening protocols in New Zealand and the need to improve them. Read Moving towards personalised breast screening in New Zealand and a second paper, Improving our breast screening protocols.
January 2020: Members of BCAC's committee **met with the newly established Cancer Control Agency, Te Aho o te Kahu**. We highlighted the need for risk stratified screening with risk evaluated through several factors including mammographic density. Key elements of our response to the NZ Cancer Action Plan 2019-2029 can be read here.
March 2021: BCAC met with **Minister of Health, Hon. Andrew Little** with **Dr Diana Sarfati, CEO** of **Te Aho o Te Kahu**. The three key issues BCAC raised with the Minister were: risk management and targeted screening for early detection and prompt treatment; improving access to medicines; and introducing precision genetic testing. Read our briefing here.
2021: Fay Sowerby wrote to **Dr Sarfati** as follow up to the meeting with the Minister (unpublished); a letter of response was received from **Dr Jane O'Hallahan** regarding this issue. Meeting held between Fay Sowerby, **Dr O'Hallahan** and **Mr Adam Stewart, National Clinical Lead of BreastScreen Aotearoa**, with ongoing communication to the present day, including this submission.
2022: Fay Sowerby wrote to **Mr Adam Stewart** seeking his feedback regarding EUSOBI's decision regarding supplementary screening for those with extremely high breast density.
https://www.breastcancer.org.nz/content/breast-density-matters
2022: BCAC's responses to **BreastScreen Review (unpublished**), Libby Burgess, Fay Sowerby and Maria Marama responded.
January 2023: BCAC responded to a call from **Te Manatū Hauora (Ministry of Health) for input on the topic of Precision Health**, which was being considered for inclusion in the next Long-term Insights Briefing to Government. BCAC's Fay Sowerby wrote a comprehensive submission, in which she describes how both precision health and precision medicine present huge opportunities for improvements in breast cancer care: *"We are on the cusp of seeing a growing range of new tools to predict breast cancer risk and to identify who needs greater surveillance using new technologies. This increased precision will direct tests and treatments to those that need them most, at the time they most need them, and result in significant improvements in both quality of life and survival".* Read our submission here.
June 2023: BCAC responded to Manatū Hauora's second consultation on its draft Long-Term Insights Briefing on *Precision Health: Exploring opportunities and challenges to predict, prevent, diagnose, and treat disease more precisely in Aotearoa New Zealand*. We outlined the wonderful

opportunities to improve healthcare for the people of Aotearoa through commitment to the development and timely uptake of innovative technologies. Read our second Precision Health response here.

March 2023: BCAC wrote a submission to the Ministry of Health on the new Women's Health Strategy, which is required by the Pae Ora, Healthy Futures Act. BCAC stressed the importance of ensuring that breast cancer was explicitly covered in the strategy and suggested three key areas needing change and better resourcing. We suggested measurement and reporting of breast density as well as provision of supplementary screening where needed, noting again that breast density both masks cancer on mammograms and is an independent risk factor and that Māori women have higher volumetric breast density than other ethnicities. Read our submission here.

These collective actions demonstrate that breast density and other issues relating to screening and earlier diagnosis have been of significant concern and some frustration to BCAC for over 10 years. We welcome the opportunity to reiterate and update our view that breast density should be measured and reported and that this information will help inform women of the importance of appropriate screening and should assist them to better understand their role and that of their whānau in decision making around this issue.

Summary of evidence-based benefits of measuring and reporting breast density

There is now ample evidence demonstrating the benefits of breast density measurement and reporting. In particular there is now recognition that:

- breast density is an **independent risk factor** that can represent higher risk of breast cancer than family history.
- **women with high breast density are not at average risk**.
- when high breast density masks breast cancer **interval cancers occur, false negative mammographic screening results are delivered and there is risk of high grade and late-stage disease.** This is causing harm to women.
- **women are willing and able to deal with any psychological issues** relating to breast density in their efforts to reduce their risk of a late-stage breast cancer diagnosis.
- taking into account combined risk for pre- and post-menopausal women **breast density is the most prevalent risk factor** and must be taken into account in **stratifying breast cancer risk.**
- **women have a right to be accurately and appropriately informed** about their physiology and health and to participate in decisions regarding their care. It is unacceptable for this information to be withheld from them.
- there is a need to **improve health literacy** relating to screening generally, including breast density and supplementary screening.
- there is a growing depth of international experience in **how to communicate issues** relating to breast density.
- there is growing recognition that decisions relating to breast density should be **discussed between doctor and patient.**
- in several countries **supplementary screening options** are becoming available and are being used **more flexibly for high-risk groups** including those with high breast density.
- there is growing recognition that **when a diagnosis is late stage and high grade**, which may occur for those with high breast density, any cost savings made at the front of the pathway from not measuring and reporting density may be balanced by **significantly greater cost as well as worse patient outcomes at the back of the cancer care pathway**.

- there is recognition that **mammographic screening**, although an excellent tool that has saved many lives, does not serve those with high breast density equally well.
- there is evidence to suggest that **deep learning (AI) and mammography** can provide efficient **risk stratification guidance** integrated into a screening pathway to help to prioritise those at higher risk of developing breast cancer to facilitate early diagnosis.
- **AI and a single reader are non-inferior to two readers**, with acceptable call backs.
- there is a growing **awareness of a two-tier system** developing – those who are informed and seek supplementary screening and those who are not and don't.
- greater precision through **AI could inform modality** selection for those most at risk.
- resistance to measuring and reporting high breast density may be a **growing cause of inequity** contributing to higher mortality for Māori and Pasifika and higher morbidity for Asian women when combined with other pathway inequities.
- there is acknowledgement that **GPs need to be better prepared and informed** to discuss breast density with patients.
- an acknowledged need for **increased or redistributed funding**, within the public health system and through health insurance, **for supplementary screening** for those with **extremely dense breasts**.
- until policy is set and funding secured, **New Zealand should follow other countries in measuring and reporting breast density**, establishing observational, retrospective and prospective studies to better serve and to better inform supplementary screening options.
- These needs sit alongside the need to **improve trust** in the system and to **improve access** so that our screening population and the health system as a whole will benefit.

Defining breast density

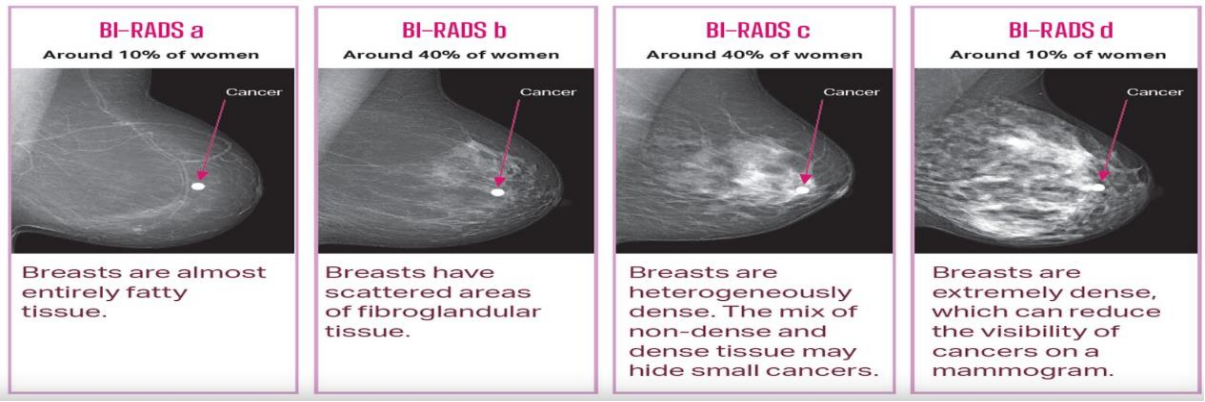
Dense breasts contain a higher proportion of glandular and fibrous tissue than fatty tissue. Dense breast tissue appears as white areas on a mammogram. As breast tumours also appear as white, the higher the density, the harder it is for radiologists to detect cancer on a mammogram. In contrast, fatty tissue appears dark on mammograms allowing easier detection of cancer. High breast density is also an independent risk factor for breast cancer.

BI-RADS scoring system

The BI-RADS (Breast Imaging Reporting and Database System) rates breast tissue for the potential presence of cancer and for density, see https://www.ncbi.nlm.nih.gov/books/NBK343794/table/ch1.t1/ and www.densebreast-info.org [15]. BI-RADS uses letters A through D to separate breast density into four groups:

- A Fatty: The tissue is not dense. 10% of the screening population
- B Scattered fibro glandular: The tissue is mostly fatty but has some dense areas.
- C Heterogeneously dense: Areas of dense tissue are present. This may make it hard to see small tumours. This occurs in about 40% of people.
- D Extremely dense: It is very difficult to see masses in the breast. This occurs in about 8 - 10% of people [3,15].

People with Bi-Rads level C and D have dense breasts. Women with dense breasts are BOTH more likely to *develop* breast cancer and more likely to have that cancer *missed* on a mammogram. Everyone's breasts are different. The amount of dense or fatty tissue varies from person to person.



These pictures illustrate the breast density categories as measured using the Breast Imaging Reporting and Data System (ACR BI-RADS® Atlas 5th Edition).

Source: https://densebreast-info.org/

What do BI-RADS number scores mean?

Doctors use a standard system to report mammogram results. A BI-RADS (Breast Imaging Reporting and Database System) number score is provided on every mammogram report to indicate whether mammogram findings are normal or abnormal. Not all abnormal findings are cancer.

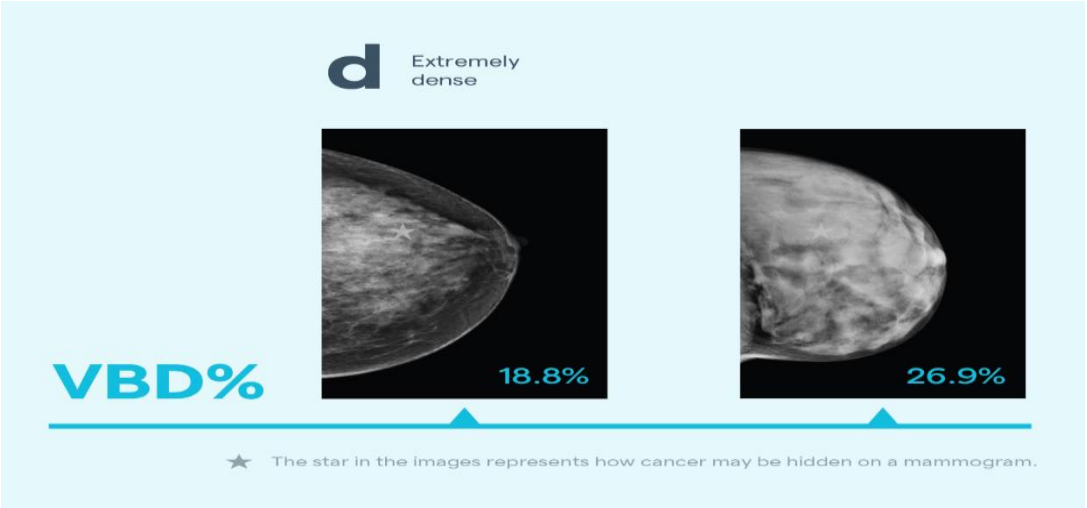
- Category 0: A score of 0 indicates an incomplete test. The images may have been difficult to read or interpret, and additional screening is required.
- Category 1: The radiologist saw nothing of concern.
- Category 2: Nothing indicates cancer, but non-cancer findings, such as a cyst, were detected.
- Category 3: Changes from your previous mammogram that are probably not cancer were identified. Your doctor may recommend additional imaging in 6 months or sooner.
- Category 4: An abnormality that looks like cancer was found and your doctor will recommend a biopsy to determine whether it is benign or cancer.
- Category 5: An abnormality was detected and is likely cancer. Your doctor will recommend a biopsy.
- Category 6: This score is used only for people who have already been diagnosed with breast cancer.

Shifting the paradigm of breast cancer detection toward earlier diagnosis and reduced morbidity for women with dense breasts appears from the evidence to be one answer to reducing the number of deaths from this disease. [72] This is not just relevant to the younger population as 28% of women older than 75 years have been found to have dense breasts and those aged 65 and older an increased risk of invasive breast cancer. [73] Breast density and life expectancy should be considered together when discussing the potential benefits vs harms of continued screening mammography in this population.

The image below courtesy of Dr Ariane Chan shows personalised volume-based measures of breast density. “Volumetric Breast Density percent” (VBD%) is a measurement of the proportion of dense tissue in the breast, on a scale of 0-100%. The two images are mammograms from different women, both judged as being in the extremely dense or “D” category.

Within category D there is still significant differentiation of volumetric density. A tumour is visible in the left view but would not be seen in the right view [16]. Lower absolute volumes of dense tissue or “percent density” is the ratio of absolute amount to the total breast volume. Typically, the

percent measures more frequently show a stronger association with breast cancer risk. Providers with Volpara automated software receive both measures.



Source: Volpara Health, 'Know your Lemons' interview with Dr Ariane Chan[16]

Evidence of breast density in New Zealand's population includes a study by Ellison-Loschmann et al., 2013, that involved 3,000 women and showed Māori women may have higher volumetrically dense tissue in their breasts than Pasifika, Pākehā and Asian women [17].

Recent international evidence has since shown that Asian women have high percent density as distinct from volumetric density [18]. It appears that quantitative measures used are important i.e., absolute dense tissue, absolute adipose tissue and percent density which has been linked through association with the HER2-enriched and luminal B breast cancer subtypes (Gierach et al, 2021) in a study of women in the Chinese population [19].

Engmann et al. (2019) found that of the over 18,000 women with breast cancer who had combined risk of over 50% for pre and postmenopausal women, **breast density was the most prevalent risk factor for both groups and had the largest effect at 39.3%** for premenopausal and **26.2%** for postmenopausal breast cancers. This study concluded that high breast density should be included in stratifying breast cancer risk for targeted preventative efforts [20].

Mammography is the established standard of care in screening for breast cancer and has been proven to reduce the mortality rate [21]. However, in dense breasts, cancers can be hidden/obscured on mammography [22,23] and may go undetected until they are larger and more likely to present with clinical symptoms [24]. Patients whose breast cancers are detected through clinical symptoms have worse outcomes than those whose cancers are screen-detected [25]. Breast density has also been identified as the most prevalent risk factor for developing breast cancer [26].

Guidelines, International Best Practice and Precedents

MRI was first proposed in guidelines for breast cancer screening in 2007 [27], only a few years after its clinical introduction. Those initial guidelines, which were generated by a committee sponsored by the American Cancer Society (ACS), have served as the template for recommendations by several organisations. They focus on patient eligibility for MRI screening using a qualifying threshold based on risk stratification. Higher risk in those patients recommended for MRI screening translates to higher cancer detection rates, which in turn impacts cost-effectiveness.

Breast density is a variable that should be included in risk stratification [20] to determine surveillance options because screening mammography may fail to detect small and developing cancers. Mammogram failure rate is a function of breast density. Density has been included in MRI screening guidelines as a risk factor but has previously been neglected when considering its role as the primary cause of false-negative mammograms. The two implications of mammograms of dense breast tissue are essentially independent: (1) refining risk stratification and (2) predicting the "miss rate" of mammography.

The designers of the ACRIN 6666 trial [28] had the same idea, with entry into their multimodality imaging study (ultrasound and MRI in addition to mammography) requiring both features, risk and density, with these two values equally weighted. The authors reported that breast density as a risk factor 'stole the show'. A response is clearly required to the serious implications of failure to detect cancer.

A study of MRI screening (Bakker, 2019) demonstrated that measuring and reporting breast density could have additional benefit for those with extremely dense breasts [29].

Appreciation of the camouflaging impact of density can be seen in Veenhuizen et al. 2021 from the **DENSE Trial Study Group in the Netherlands** [30]. This prospective, randomized trial reported a statistically significant **lowering of interval cancers, the primary endpoint**, while mortality data will be forthcoming. This is important because for every 1000 women screened, **although we save 8 lives, we lose 16 and it is these 16 lives we need to focus on**. Undergoing supplemental MRI screening (**which could be abbreviated MRI or other affordable options**) reduces the frequency of interval cancers by 84**%, thus effectively reducing underdiagnosis**. The Positive Predictive Value (PPV) of MRI prompted biopsy was 26.3%, which was seen as acceptable with a similar PPV of biopsy reported for mammography. That MRI detects breast cancers earlier is apparent from the number of cancers detected in the regular population of women with extremely dense breasts at the subsequent mammographic screening. This is around 2.0/1,000 after MRI, compared with 6.8/1,000 without earlier MRI. Furthermore, the next MRI screen (2 years later) yielded a supplemental detection rate of only 5.9/1,000, all of which were stage 0/1 and node-negative; providing further evidence that relevant cancers are detected predominantly earlier. The PPV remained stable (PPV = 23.5% in follow-up) [30]. The results of the DENSE trial were then modelled in a microsimulation model (MISCAN) to determine the long-term impact of offering breast MRI screening to women with extremely dense breasts [5]. Different scenarios were explored. The results suggested that by adding biennial MRI to biennial mammography—as was performed in the DENSE trial—would save 8.6 additional lives per 1,000 women invited, at a cost of 150,00 EUR per life (252K NZD), or 22,410 EUR (37,350 NZD) per quality-adjusted life-year (QALY). With modelling they found using MRI alone once every 4 years could be regarded as the most cost-effective screening strategy. This would save 7.6 additional lives per 1,000 women screened at a cost of 74,700 EUR (124,500 NZD) per life or 11,454 EUR (19,090 NZD) per QALY. In practice, MRI alone with a frequency of once every 2 to 3 years may be preferred to prevent non-detection of rapidly growing cancers, although a higher frequency may also lead to a somewhat higher false positive rate. As the costs of MRI screening are mostly influenced by the cost of the MR scans [31], there is strong interest in breast MRI with shorter scan protocols.

Abbreviated MRI has a cancer detection rate of 11.8 cancer /1000, specificity of 86.7% can have a similar success as the standard MRI protocol that was used within the DENSE trial. Moreover, the study provided further evidence that in women undergoing MRI for screening, the additional contribution of x-ray-based breast imaging is very limited [5]. This may enable a higher throughput and therefore a lower cost per examination.

These trials concluded that those with high breast density are underserved by screening with mammography or digital breast tomosynthesis (DBT) alone stating that the evidence applies to both those with heterogeneously and extremely dense breasts although for those with heterogeneously dense breasts the risk benefit ratio will differ.

A statistic quoted by Ritse Mann, is that according to epidemiological modelling from the DENSE trial results, **when dying from breast cancer is prevented by MRI, a woman gains on average 15 years in good health**, before she dies of another cause. **This is the inverse of a statistic an oncologist may provide should women be diagnosed late-stage high grade from an interval cancer**. Knowing that an MRI or similar technology (Abbreviated MRI or CEM) could save you 15 years without quality-of-life impacts may influence a consumer to want to have access to screening. This information should clearly be available for shared decision making regarding supplementary screening options [3].

Based on the work of Dr. Christiane Kuhl who has been using MRI to screen the general population at baseline risk, as well as the findings from the DENSE trial, the European Society of Breast Imaging in 2022 recommended MRI screening in women with extremely dense tissue (Level D), independent of other risk factors, to be performed every two to four years (see Appendix 1). **This marks the first time the "miss rate" in high-density patients has driven MRI screening guidelines.**

Available evidence now points to very few interval cancers emerging if the new European Society of Breast Imaging guidelines of "MRI every two to four years" is followed for Level D patients.

Those who led the trial now look to those of intermediate risk. The European recommendations were debated at EUSOBI 2023 by Dr Ritse M. Mann of Radbound University Medical Centre and the Netherlands Cancer Institute and Dr Marc Lobbes, Department of Medical Imaging, Zuyderland Medical CentreSittard-Geleen and Maastricht University, Netherlands. During the "The Pro's and Cons of Breast Screening" discussion Dr Mann stated, "Breast MRI is proven effective in intermediate risk for the development of breast cancer and was shown to be affordable in both women with a familial risk and those with extremely dense breasts." His view is that "CEM is not and it will take years to gain the evidence, **CEM while a vital alternative for when MRI is not feasible**, it does simply not appear to be as good [32].

In contrast Dr Marc B.I. Lobbes stated "the literature on CEM is scant but is looking good so far. New trials have been initiated e.g., CMIST and BRAID trials and therefore it does not seem to be an issue of whether CEM should be considered but **where it should be considered and in what specific population**". [33]. CEM provides some advantages over MRI. It has high sensitivity relative to Mammography and ultrasound of 15.5 per 1,000 but lower specificity (76% vs 91%). It is more affordable, removed the issue of claustrophobia, metal implants or gadolinium contrast but some may be allergic to the iodine contrast used for CEM unless well managed. It also requires skills not needed for mammograms and ultrasound. [73]

Currently, breast screening guidelines in the United States emanate from several organisations, differing only by minor variations now that **The U.S. Preventive Services Task Force has recently recommended all women start getting regular mammograms at age 40**, instead of 50, the previous recommendation [34].

National Comprehensive Cancer Network (NCCN) have now published new guidelines [35] Guidelines Detail (nccn.org) ; https://www.nccn.org/professionals/physician_gls/pdf/breast-screening.pdf (free membership and login required for access). See also Appendix 2. The new guidelines are **based on individualized density levels** and **predict the potential benefit of MRI or other screening modalities, along with risk stratification that optimizes cancer detection rates.** For average risk

women, the screening guideline includes: **"Consider supplemental screening for those with heterogeneously or extremely dense breasts."** For women at increased risk, "Consider contrast-enhanced mammography (CEM) or molecular breast imaging (MBI) for those who qualify for but cannot undergo MRI. Whole breast ultrasound may be done if contrast-enhanced imaging or functional imaging is not available/accessible." **These are very practical guidelines that recognise affordability is an issue.**

Finally, a new prospective study of over 10,000 women over 10 years (2008-2020) in April 2023 reported the association between change in mammographic density in each breast over time and risk of subsequent breast cancer [36]. This study found that **the rate of change in breast density was associated with the risk of subsequent breast cancer. When one breast had a slower decline in breast density than the other, it was more likely to develop breast cancer.** Public-health researcher and study co-author Shu Jiang is of the view that incorporation of longitudinal changes into existing models could optimise risk stratification and **guide more personalised management** and proposes that these measures enter clinical use as soon as possible. **This finding suggests novel benefits to be gained from measuring and reporting density as this difference may well be a new biomarker of risk that could enable early diagnosis.**

Regional and Country Screening Protocols and AI Initiatives

Europe and EUSOBI Recommendations

Breast Density notification: ten of twenty-two countries (as reported by DenseBreast-info) record breast density in medical mammography reports [15]. Belgium, Israel, France and Italy are also participating in the My Personalised Breast Screening study (myPEBS), led out of the UK to investigate whether a more personalised approach may be beneficial (further details below). https://radiology.medschl.cam.ac.uk/research/research-themes/breast-imaging/mypebs-my-personal-breast-screening/

Population based breast screening guidelines vary across Europe. In some countries (e.g., Austria, Croatia, Hungary, France, Serbia, Spain, Switzerland) screening guidelines for women with dense breasts include that they be offered supplementary ultrasound following a mammogram [37].

Following recent MRI screening trials evidence is accumulating that confirms that women with dense breasts are underserved by screening with mammography alone [21, 26]. In March 2022, new guidelines were issued in *Breast cancer screening in women with extremely dense breasts by the European Society of Breast Imaging (EUSOBI)* (see Appendix 1). These highlight the growing evidence, particularly the results of a randomised, multicentre controlled study, the Dense Tissue and Early Breast Neoplasm Screening (DENSE) Trial [21, 26].

The European Society of Breast Imaging 2022 recommendations now advocate for tailored screening programmes, stepping away from the one-size-fits all approach of mammography that is still in use by most European screening organizations. **There is compelling evidence that the new recommendations will enable an important reduction in breast cancer mortality for women with dense breasts.**

Summary of the EUSOBI Recommendations
EUSOBI's summary graphic of the recommendations (Appendix 1) highlights:

- Supplemental screening is recommended for women with extremely dense breasts.

- Supplemental screening should be done preferably with MRI. Where MRI is unavailable, ultrasound in combination with mammography may be used as an alternative.

In addition to recommended additional screening in women with extremely dense breasts, **EUSOBI recommends that *"women should be appropriately informed about their individual breast density* in order to help them make well-balanced choices**."

EUSOBI acknowledges that it may take time before the new recommendations are implemented in Europe and that the level of implementation is dependent on the resources that are available locally.
It is important to emphasize that the EUSOBI recommendations have not yet been adopted as guidelines across Europe. However, it is hoped that national breast screening committees will aspire to implement these recommendations as soon as possible to benefit women.

Key messages:

- Breast density can both hide cancers on a mammogram and increase the risk of developing breast cancer.
- Women with dense breasts benefit from additional screening tests after their mammogram.
- Breast density education and access to supplemental screening can mean the difference between early or late-stage diagnosis.
- Physicians should be educated and prepared to have patient conversations about breast density.
- For more information about Dense Breasts visit: DenseBreast-info.org/Europe

Prof. Christiane Kuhl, co-author of the EUSOBI Guidelines, states that radiologists must be more active in providing objective and understandable information to women about the diagnostic and prognostic implications of dense breasts, and the value of using other screening methods[38] (March, 2023).

Dr Wendie Berg along with EUSOBI's Matthias Dietzel discusses improving early detection of breast cancer by implementing current guidelines and technologies in a YouTube video available HERE. At the end of the video, Dr Berg simplifies and provides practical responses to the challenges posed [39,40].

AI initiatives

Please refer to the AI section (p. 26-31) for an AI overview. These initiatives indicate that Europe is highly active in enhancing breast screening outcomes and improving productivity through AI.

Denmark: The Danish Capital Region breast cancer screening programme following a retrospective trial decided to adopt their AI algorithm in clinical practice and evaluate it on an ongoing basis (MAGIC – MammGraphy AI in Breast Cancer diagnostics). An AI score 1–5 is single-read, AI score 6–10 requires double reading, and where the AI score is > 9.98 the woman will be recalled to assessment based on AI only. Preliminary results presented at the meeting are very encouraging [12].

Germany: The PRAIM Study (PRospective multicentre observational study of an integrated Artificial Intelligence (AI) system with live Monitoring) is ongoing to prospectively investigate double reading versus single reading + AI algorithm, within a cohort of 400,000 women (age 50–69 years) participating in the German Mammography Screening Programme [12].

Spain: A recent retrospective study consisting of mammography exams from the Cordoba Tomosynthesis Screening Trial demonstrated that **an AI algorithm reduced workload up to 70 % without reducing sensitivity by 5 % or more** [29]. From the results of this study, the AITIC trial (Artificial Intelligence in Breast Cancer Screening Programs in Cordoba) was designed. This prospective trial among 27,000 women (age 50–69 years) will investigate double reading versus reading strategy based on score provided from the AI algorithm: score < 8 (low probability of cancer) will not be evaluated by any radiologist, score > 7 double reading.

Sweden: In Sweden there are currently three independent ongoing prospective trials investigating incorporation of AI algorithms in mammography screening. The *MASAI* (Mammography Screening with Artificial Intelligence) study is a randomized-controlled trial investigating double reading (control arm) versus single reading + AI algorithm (intervention arm) among 100,000 women (age 40–74 years). In the case of AI score 1–9 single reading will be performed, AI score 10 will require double reading. Results of the study demonstrated a higher recall rate in the intervention arm of 2.2% versus 2.0%, including a higher cancer detection rate in the intervention arm (6.1% versus 5.1%, P = 0.052) [12].*The second trial* is the ScreenTrustCAD (Artificial Intelligence in Large-scale Breast Cancer Screening) observational study investigating double reading versus single reading + AI algorithm versus AI alone (only for secondary endpoints: reader flagging, consensus recall, process failure) among 55,579 women (age 40–74 years). Preliminary results presented at the annual meeting of Radiological Society of North America in 2022 showed that combining the evaluations of one radiologist with AI compared to two radiologists improved cancer detection rate (relative true positive fraction 1.06 (95% confidence intervals: 1.01–1.10) without an increase in recall rate (28.0/1000 versus 29.3/1000). It was concluded that **replacing one radiologist with AI is ready for clinical implementation in mammography screening programs.**
The third trial is the observational AI-ROL study (Artificial Intelligence in Breast Cancer Screening in Region Ostergotland Linkoping) investigating the use of AI algorithm as third reader as well as a decision support system during consensus in a cohort of 15,500 women (age 40–74 years). The primary outcome measures are cancer detection rate (CDR), referral rate and positive predictive value (PPV) of referrals, with PPV of Transpara AI scores as a secondary measure. The secondary outcomes are PPV for referrals, biopsies and Transpara scores [12].

United Kingdom

NHS Breast Screening Programme

Currently in the UK, population routine screening mammograms are offered to women aged 50–74, every 3 years. Although dense breasts affect the likelihood that a cancer will be masked and increases a woman's risk for developing breast cancer, density is not yet an element of UK data collection. A woman's breast density is not assessed, not recorded in medical records, nor reported to her. For diagnostic purposes, this may differ. Asymptomatic women attending routine national breast screenings receive mammography alone. There are however several trials occurring in the UK focussed on risk stratification and screening age [41].

MyPeBS, a randomised trial utilising the CanRisk (BOADICEA) tool

This large-scale study currently being undertaken in Belgium, France, Israel, Italy, and the UK is led by Fiona Gilbert of Cambridge University. MyPEBS investigates varying the approach to breast cancer screening based on individual women's risk of developing breast cancer. Consenting women will be randomised into one of two arms in the study, either receiving standard screening or the personalised programme. **Women in the personalised programme found to be at higher risk will receive more regular mammography scans, with those at the highest level of risk also receiving**

MRI scans. Women at **low risk** will have mammography scans **less frequently**. Ultrasound scans will also be given to women found to have high breast density, which may obscure small lesions in mammography and is in itself a risk factor. For more information see **BRAID trial** (https://radiology.medschl.cam.ac.uk/research/research-themes/breast-imaging/braid-trial/) [42]. A woman's level of risk will be assessed based on **genetic factors and breast density** as well as **personal and familial health history** provided through questionnaires. With information updated on a yearly basis, it is possible that the categorisation of an individual's risk may be altered. MyPeBS will investigate whether there are benefits to a personalised approach compared with the standard one. https://radiology.medschl.cam.ac.uk/research/research-themes/breast-imaging/mypebs-my-personal-breast-screening/ [43].

UK AI Initiatives

In the United Kingdom Life Sciences Innovate UK funded two AI companies, Kheiron and Alphabet Inc, to undertake prospective testing in NHS screening. The Kheiron retrospective trials 1 and 2 in Hungary and England confirmed the utility of AI and underpinned the CE mark for safety and quality, with a further study undertaken in Scotland [32,33]. The ARIES multisite retrospective study is being analysed. The prospective LIBRA trial is a single site paired study with AI as a third reader and used in arbitration with no prompts. The GEMINI service evaluation is comparing standard double reading and AI as a third reader and consensus using prompts in Aberdeen, Scotland with a larger multi-site evaluation in England with 200,000 women. Google is working on two studies focused on different use cases.

In the UK, the AI in Mammography Screening (AIMS) study is currently running at two NHS Trusts to determine the feasibility and impact of introducing AI as a second reader within a double reader workflow, and to understand the important aspects of human–computer interaction when breast cancer specialists in an arbitration panel include AI outputs in their decision making. Results from this study are expected in 2024 [12].

Ireland

BreastCheck – the National Breast Screening Programme in Ireland screens women aged 50 to 69 years using routine mammogram. Screening takes place at mobile and static units across the country. Around 70% of eligible women choose to be screened. A retrospective research project established in March 2022 between RSCI and BreastCheck has recently been postponed. There was a hope that the data generated would provide measurements of breast density among women who attended screening between 2008-17 to understand the implications for breast cancer risk characteristics. The aim was to learn about this radiological feature and compare density measures from women who were diagnosed with breast cancer through BreastCheck, with women who have not been diagnosed with cancer. The project will not look for cancer or perform clinical reviews [44].

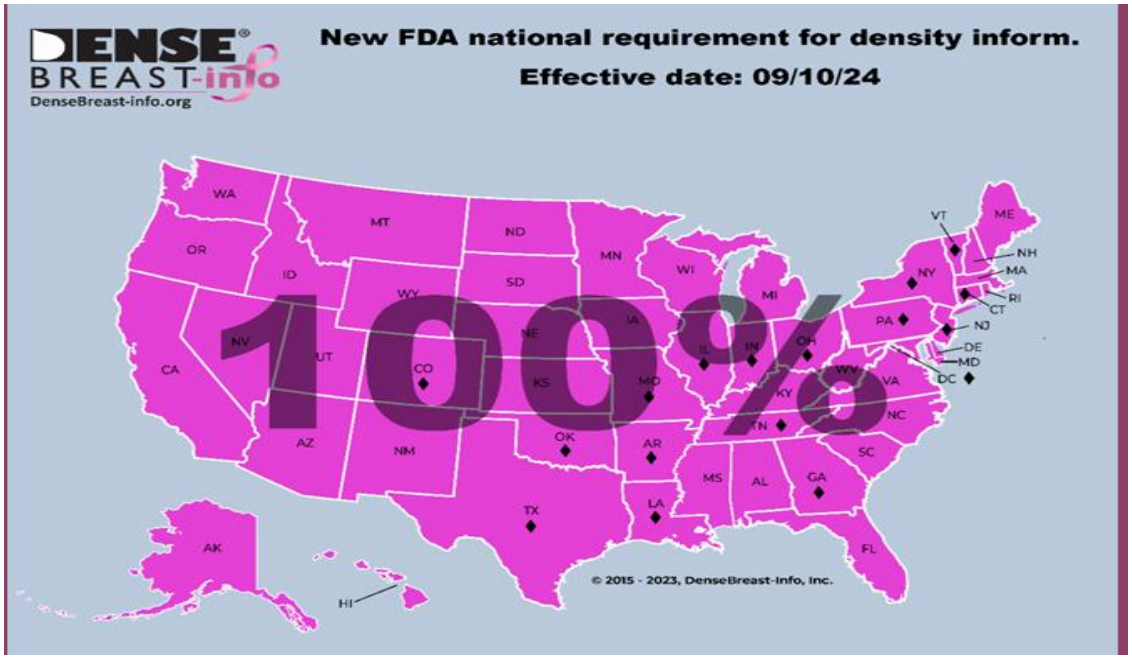
Sibohon Freeney, breast density advocate, states that women in Ireland are repeatedly and routinely refused access to their personal breast density Information although it is a visible feature on mammograms.

United States of America

On 8 June 2023 new FDA guidelines for mammograms were announced which will be implemented by September 2024. Current FDA guidance requires hospitals and breast centres to give people information about their breast density with their mammogram results. Some hospitals and breast centres already provide this information. Connecticut was the first in 2009, followed by 38 States and

the District of Columbia. 6 of these just require a general notification. **Over 90% of American women now live in a State with some level of density notification.** [73] By September 2024, mammogram providers will be required to inform patients with dense breasts that they should discuss the need for additional imaging [6].

The FDA now requires that breast density be included in a mammogram report on the basis that women with dense breasts have a higher probability of getting breast cancer and because dense breast tissue makes it more difficult to find breast cancer on a mammogram. Women will be told that knowing about their breast density as well as other risk factors can help them and their doctor decide whether they should have additional screening that may include a breast ultrasound or MRI.



By September 10, 2024, patients must be sent one of two density notification statements ("not dense" or "dense"), and the mammogram report sent to referring providers must include an assessment of the patient's breast density.

Source: https://densebreast-info.org/legislative-information/national-reporting-standard/

They will be advised that their mammogram report will have two scores.

- A number score between 0 and 6 which indicates the finding on the mammogram, such as nothing of concern, non-cancer findings or abnormalities.
- A letter score of A to D indicating their breast density. A and B means their breasts are not dense while C and D means they have dense breast tissue.

What changes with the FDA's update?

The 2023 FDA update is a significant change for many hospitals and clinics. This change is the result of years of advocacy by healthcare professionals and people with dense breasts whose cancers went undetected by mammograms. This change was planned for 2020 but was deferred due to the COVID 19 pandemic. The FDA will work with hospitals and clinics to ensure they provide and read mammograms correctly.

Changes in practice

People will be encouraged to talk with their doctor or other healthcare provider to learn what type of screening is recommended based on their personal, family medical history and breast density. They will learn about the benefits, risks and costs of additional screening so that they can make a decision that is best for them.

People will be told that doctors will help them understand the impacts of other risk factors, such as a history of pregnancy and breastfeeding, alcohol use, obesity, family history or having a gene mutation that increases breast cancer risk.

Some with a genetic mutation that puts them at higher risk for breast cancer may already undergo additional screenings, including MRI. It will be explained that doctors can spot cancer that may not be seen on a mammogram with MRI or ultrasound. However, they will still need to have an annual mammogram.

The Find it Early Act, USA

In addition to the FDA's requirement that breast density be measured and notified the US federal bill "Find It Early Act" was introduced to the 117th congress 2D session H.R. 9505, Dec 2022 to provide for **expanded insurance health coverage with no cost sharing for additional breast screenings** for certain individuals at greater risk for breast cancer, **including those with dense breasts**. Information can be found on DENSE Breast Info [45].

The WISDOM Trial

WISDOM is a randomised and adaptive trial incorporating choice evaluating optimal frequency of screening. Laura Esserman and Athena investigators established the WISDOM (Women Informed to Screen Depending on Measures of risk) trial in the **USA** to answer two questions: whether it is better to screen annually or biannually, and whether women are best served by beginning screening at 40 or some later age given current age ranges are based on data generated several decades ago. They recognise cancers vary in timing of onset, rate of growth, and probability of metastasis. They saw an opportunity to investigate tailored screening based on a woman's specific risk for a specific tumour type, generating new data that can inform best practices. WISDOM is a pragmatic, adaptive, randomized clinical trial comparing a comprehensive risk-based approach to traditional annual breast cancer screening. The multicentre trial is powered for a primary endpoint of **non-inferiority with respect to the number of late-stage cancers detected**. The researchers will adapt the approach as they learn who is at risk for what kind of cancer. WISDOM is the product of a multi-year stakeholder engagement process that has brought together consumers, advocates, primary care physicians, specialists, policy makers, technology companies and payers to help break the deadlock in this debate and advance towards a new, dynamic approach to breast cancer screening [68,69].

USA AI Initiatives

In the US, a study has been completed at Northwestern in Chicago looking at the feasibility of using AI to triage women with suspicious lesions for same-day diagnostic workup [12].

The Mirai model: A team of scientists from MIT's Computer Science and Artificial Intelligence Laboratory (CSAIL) and Jameel Clinic demonstrated a **deep learning system to predict cancer risk** using just a patient's mammogram. Implemented at Massachusetts General Hospital during the COVID pandemic to help to prioritise which patients should be screened first when a backlog had developed, the model showed significant promise and even improved inclusivity: it was equally

accurate for different ethnicities. The group is now involved in large-scale validation across several hospitals and technologies and has been validated on breast screening data sets from 7 different countries. From a total of nearly 129,000 mammograms taken from over 62,000 patients that detected 3,815 cancers, Mirai obtained concordance indices (AUCs) of between 0.75 and 0.82 across the seven sites for cancers detected within 5 years of screening, [67,71]. This compares favourably with an AUC of 0.62 from traditional risk models such as Tyler-Cuzick. This model has been found to identify those at risk of cancer in the next 3-5 years. .

Other AI deep learning models in the United States include Profound, iCAD, Inc, Nashua, NH which have also been used to identify risk factors beyond breast density to improve prediction of interval cancers. [73] p4.

Japan

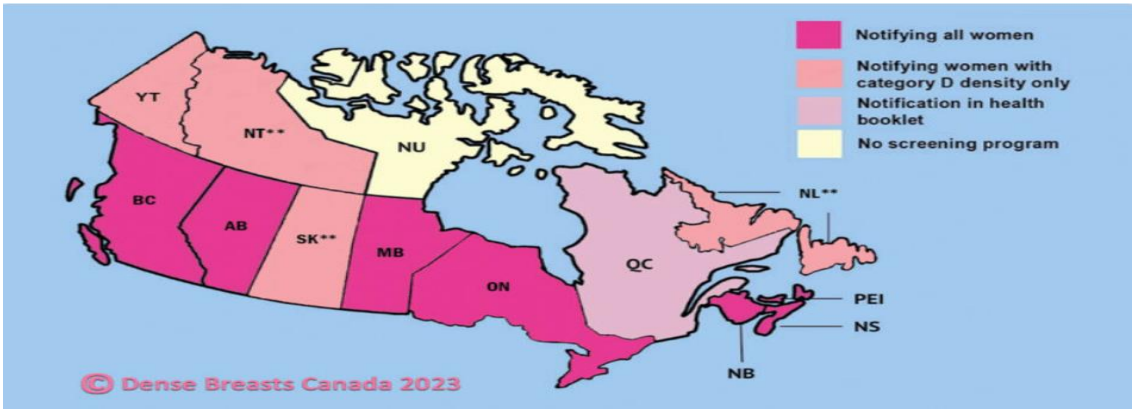
Breast density notification is not officially recommended, however in 2017, 15.7% of municipalities were measuring and recording density [46].

South Korea

The AI-STREAM (Artificial Intelligence for breast cancer screening in Mammography) study is a prospective trial investigating single-reading versus single-reading + AI algorithm (computer aided detection/diagnosis) in a cohort of 32,714 women (age 40–80 years) participating in Korean breast cancer screening programme at five sites. Standalone AI will be tested in the background. Arbitration will also be examined separately where a third reader will decide without AI prompts [12].

Canada

In 2023 Ontario, Canada's most populated province, became the 7th province to require notification about breast density to women after screening mammography. Women will be informed of their specific density category (A, B, C or D) and the associated risks. Further, a draft recommendation to provide supplemental screening for women in category D (extremely dense breasts) is expected to be finalized in the fall of 2023. Two additional provinces, Saskatchewan and Newfoundland-Labrador have also committed to begin breast density notification in 2023. That will bring the total number of provinces with some level of density "inform" requirement to 9 out of 10 [15].



Source: https://densebreast-info.org/density-inform-in-canada/

Australia

There is a growing demand for BreastScreen Australia to notify women who have dense breasts and offer more testing for those at most risk [10]

BreastScreen Australia's 2020 position statement on breast density screening states that BreastScreen Australia should not routinely record breast density or provide supplemental testing for women with dense breasts. Despite this, Western Australia has had density notification and reporting for several years [9] and BreastScreen South Australia recently decided to measure and report breast density [8].

Assoc. Professor Vivienne Milch, Cancer Australia, says BreastScreen Australia will conduct an evidence review on supplemental screening for women with dense breasts some time in 2023, although there is no guarantee of a policy change. "We're aware of the growing momentum of advocacy and of also some women's desire to know their breast density", adding that different states have different policies. "Western Australia has been telling women about their breast density for some time, and then there are pilots in some services (Queensland and South Australia). We may or may not have a policy change. But we'll be looking at the evidence."

Professor Bruce Mann, who works with the "Roadmap to Optimising Screening in Australia" (ROSA) project [47], says there is enough evidence to justify a change to BSA's screening regimen. "As women and the community become more informed, there is a danger that what is offered by BreastScreen will be seen as insufficient," he said, "which will lead to women opting out of BreastScreen and going privately. **What we don't want in this country is a two-tiered system where those who know and can get the best, do, and everyone else gets what's offered to them. That's what we are working to avoid**."

"In early 2023 after additional stakeholder consultation ROSA submitted a final set of recommended actions and an updated 5-year Roadmap designed to **guide Australia towards risk-based breast cancer screening.** These recommendations and Roadmap draw on key findings from the ROSA technical work combined with the advice of an independent multidisciplinary Expert Advisory Group, an extensive network of co-opted experts, and input from senior BreastScreen state and territory personnel. The recommendations and Roadmap are presently under consideration by the **Australian Government Department of Health and Aged Care**" [47].

Prof. Mann recently said **"If you can show that by doing something different you are finding more cancers, fewer cancers are being diagnosed between screening rounds, and the stage, the size and the nodal status of cancers that are diagnosed is moving in a favourable direction, I believe that's sufficient to encourage implementation with a planned review in 10 years when the mortality information's there"** [10].

He acknowledges that growing demand has been partly stimulated by the FDA in the US having recently mandated that women be notified by mammogram providers if they have dense breasts, giving them the opportunity to arrange supplemental testing.

Dr Sandy Minck, a GP and breast density awareness and notification advocate, said she was "dumbfounded" by the BSA position statement. "As a consumer I'm outraged. As a health professional, I'm dumbfounded. I just don't understand it" [10].

In Australia it has also been clearly demonstrated, through recent research that shared decision-making between women and their GPs is essential for informed decision making. A study found

more than 90 per cent of respondents would like to be and continue to be informed of their breast density, with **just two per cent** preferring not to be told as part of their future appointments. **It also found 65 per cent of respondents strongly agreed or agreed that knowing their breast density meant they felt more informed to make decisions regarding their breast care** [8].

There was also a separate **independent study** that showed that **80% of women screened want to know their breast density**. This cross-sectional study conducted at Adelaide's Queen Elizabeth Hospital Breast and Endocrine Clinic outpatient department has highlighted the **overwhelming majority of women do not know their breast density**, as reported in May 2023. Women waiting for their mammogram were given a breast density survey to complete. It was found that of the 300 patients surveyed **40% had not heard the term 'breast density' before**. Of those who had heard of breast density, 29% knew it could increase risk of breast cancer and 70% knew it could mask breast cancer. Thirty-three per cent of women who had heard of breast density were aware it could not be determined by touch or feel. Among all respondents, 80 per cent were interested to know their own breast density [48].

At the Royal Australasian College of Surgeons Annual Scientific Congress in Adelaide (1-5 May 2023), Dr Bhattacharjee presented research results and stated "**It's time we had a serious discussion about the benefits of breast density notification and whether it should become a compulsory component of breast cancer screening reports for all Australian women**." The Congress is the largest multi-disciplinary surgical meeting held in the southern hemisphere and brings together some of the top surgical and medical minds from across Aotearoa New Zealand, Australia and the rest of the world.

BreastScreen SA Clinical Director, Associate Professor Michelle Reintals, reiterated that higher breast density has been linked to an increased risk of breast cancer and can reduce the visibility of breast cancers on a mammogram. "While it is common and normal to have high breast density, this knowledge is important as it can inform decisions around breast care and increase breast awareness. It is important to recognise that regardless of an individual's breast density, mammography is still the best breast cancer screening test, with regular screening reducing the chance of dying from breast cancer by up to 40 per cent" [49]. She led a research study reporting Breast density in a population-based screening programme called the BreastScreen South Australian Breast Density Reporting Trial, https://www.breastscreen.sa.gov.au/health-professionals/breast-density-research. The BSA Commonwealth and State Health Minister approved this trial. The 6-month pilot, utilised Volpara software across 3 locations, for 40-64 and 65–74-year-olds. A significant communication programme ran alongside the pilot. Integrating Volpara software was initially challenging but critical to success. The initial data reported was surprising in that on the Bi Rads scale 26.5 % were category A (fatty tissue, low density), 42% were category B, **23.9**% were category C (heterogeneously dense) and **7.9** % were category D (extremely dense) which indicates those with high density were just over 31% in total and not the expected 50% in the combined higher category. There were variations by site but the pattern was similar.

A recent Australian study highlights the fact that **General Practitioners need support to be able to have discussions with their patients about breast density**, and there are now several templates for this [50].

Western Australia

Western Australia has for several years measured and reported breast density [51].

South Australia

From 8 August 2023 BreastScreen South Australia joined Westen Australia as the only Australian states to report breast density measurement [8,9].

It is common, however, for radiology providers outside the screening program to routinely report breast density in the mammogram report.

In Australia, women seeking supplemental screening can be referred for breast imaging or a breast specialist opinion, but there may be financial implications. Private radiological services will accept referrals for supplemental screening investigations such as breast ultrasound and breast MRI.

Queensland

BreastScreen Queensland, Sunshine Coast is conducting a randomised controlled trial to assess the effect of notifying women participating in population-based breast screening of their breast density on their psychosocial outcomes and health services use [52].

This trial includes 3 arms that will be compared amongst women with dense breasts determined from the mammogram:

1. standard care in BreastScreen Australia, i.e. no notification of breast density
2. notification of breast density plus a hard-copy written health literacy sensitive information insert
3. notification of breast density plus a link to an online video-based health literacy sensitive information via a page on the BreastScreen Queensland website, visible only to study participants.

The additional health literacy sensitive information provided to participants includes a brief explanation of breast density, suggested actions participants could take, and a discussion of the risks and benefits of those actions. The actions include being more 'breast aware' and discussing possible additional testing with a General Practitioner (GP). Information to help inform discussions with patients is available for GPs.

The woman's nominated GP will be provided with the participants' mammogram results as per standard BreastScreen Queensland process (that is, only if the woman has provided her GP's details to BreastScreen Queensland). GPs will also be provided with the breast density results of participants in trial arms 2 and 3 (participants who receive their breast density results). For women in Arm 1 who do not receive a breast density notification, as per usual care their respective GP will also not receive the breast density result. For women who don't have a nominated GP, participants may still discuss their mammogram results including breast density information and the trial with the GP they choose to visit. If needed, these GPs can call BreastScreen Queensland Sunshine Coast Service and request additional information or may contact the study researchers at The University of Sydney. Research participants will be asked to take three surveys online as follow-up for outcomes over two years. Each survey will take less than 10 minutes to fill out.

The findings of this study will show the immediate and long-term impact of breast density notification on women, GPs, and screening services and will help inform future policy and practice decisions on this important issue. To participate in this study, eligible, asymptomatic women aged 40 to 74 years need to book a screening mammogram at a BreastScreen Queensland, Sunshine Coast

Service location. These include Nambour, Caboolture, Caloundra, Gympie, Maroochydore, Noosaville, the Sunshine Coast University Clinic, and various mobile van locations.

BreastScreen Queensland Sunshine Coast Service will use the fully automated software, Volpara, to measure breast density.

BreastScreen Queensland is conducting this study in partnership with researchers and clinicians at The University of Sydney. For more information from the researchers, please contact: Dr Brooke Nickel +61 2 9351 7829 or email breastdensity.study@sydney.edu.au [52].

Insurance

Medicare in Australia has recently changed the criteria for its risk assessments to not only include family history and lifetime risk but to also provide an option considering other risks including breast density, to allow women with greater than 30% lifetime risk to gain funding for an MRI or ultrasound. Supplemental breast ultrasound screening may also be available through medical imaging departments. Nurses at certain BreastScreen sites can be contacted for additional information about referral pathways for women with dense breasts.

Summary of Australian situation

After many years the tide is turning in Australia towards measuring and reporting density. This is being managed differently state by state but ROSA's recommendations for a roadmap towards risk-based breast screening to the Australian Government Ministry of Health and Aged Care may extend the current changes. These focus in the first instance is on breast density measurement and reporting and may move to one which takes into account all risk factors in determining screening protocols. BreastScreen SA Clinical Director, Associate Professor Michelle Reintal, Professor Bruce Mann and Dr Avisak Bhattacharjee are of the view that **Consultant Surgeon and Surgical Epidemiologists' leadership and courage to stand up will be critical in improving screening protocols**. They noted the courage and leadership of those in Europe and the US and acknowledged that making this change will add value to health outcomes.

New Zealand

New Zealand's BreastScreen Aotearoa (BSA) provides mammograms to women aged 45–69 every two years.

There is a separate pathway outside the BSA screening programme for those known to be at high risk and those who find their cancer symptomatically.

Although dense breasts affect the likelihood that a cancer will be masked and increase a woman's risk for developing breast cancer, breast density is not currently an element of New Zealand's data collection. A woman's breast density is not assessed, not recorded in medical records, nor reported to her unless she specifically asks. We are aware, however, that private providers are reporting a density measure or estimation to women and advising how to manage their increased risk of breast cancer, including with supplemental screening. We are also aware anecdotally that BSA may be providing ultrasound on occasion, but we do not know how consistent this approach is.

Insurance: Southern Cross in New Zealand unlike access to Medicare in Australia do not currently take breast density into account in determining whether an MRI is necessary, their focus is on

genetics and family history. To receive an MRI a specialist breast surgeon referral is needed, a GP cannot refer a patient for MRI.

BCAC is concerned that inequity is present and developing further in Aotearoa as information on breast density is provided in private clinics and additional screening offered in some. BreastScreen Aotearoa's publicly funded screening programme needs to address this issue for women accessing the programme so that inequity does not develop further.

The RANZCR College reporting guidelines for mammography recommend that breast density be listed in the mammogram report. **They go on to say this is not implemented in the BreastScreen programmes in Australia or New Zealand, where a formal report is not issued.** Of note the RANZCR Breast Density Position Statement has been removed from the RANZCR website (October 2023) which states that the Breast Density Position Statement is being updated, "Should you require any information on Breast Density Imaging please contact Standards@ranzcr.edu.au". Following the FDA's ruling we hope a new statement will be more representative of the evidence and the importance of breast density measurement and reporting to women's health.

New Zealand consumer view

BCAC's recent Precision Health Submissions stated, "In New Zealand breast cancer consumer organisations want to see breast density measured and reported to reduce late-stage diagnosis, as well as knowledge and protocols developed for how to respond to this need." We have advocated on this issue for many years [1, 2]."

Based on BCAC's Fay Sowerby's response to the BreastScreen Aotearoa and associated Epidemiological Review (shown below in part only)
Fay indicated that the review supported the status quo but was equivocal in commentary relating to potential ways the programme might be optimised, with its emphasis on access and coverage.

Recent randomised, observational, retrospective and prospective trial outcomes and research have reinforced the opportunity to optimise population-based screening programmes through risk stratification using new technologies and Artificial Intelligence (AI). At the very least we should be gathering this information to gain a better understanding of our unique population. Watching these changes being made globally is hard when there is no real opportunity to fully engage on these issues locally. We struggle to understand the vision or plans for change, outside the status quo. **A focus on earlier diagnosis particularly for Māori and Pasifika and other underserved populations is a priority**. We recognise that these groups will also benefit from broader research and improvements regarding quality, safety and mortality for all.

How to optimise further by measuring and reporting density
There is global evidence indicating further optimisation will be achieved when women with high mammographic density are informed of their density and further benefit when they are offered supplemental screening.

Measuring and Reporting Density: In the BSA Review epidemiology report a discussion regarding breast density concludes there is "no benefit to be gained" from measuring and reporting density although it does suggest equivocally that a discussion would be helpful. I note this issue has not been picked up by the BSA Review document itself. This is at odds with global research and evidence, advocacy and developing practice. By not measuring and reporting density there is also a **lost opportunity for research in our unique population to develop greater understanding of ethnic diversity, which is particularly important given the poorer breast cancer outcomes for Māori and**

Pasifika women in Aotearoa. We also lose the opportunity to achieve earlier diagnosis and to thus reduce mortality. The advocacy we hear from New Zealand women is getting stronger and stronger.

Consumers are concerned that responses are slow to the flow of information from outside New Zealand either through NSU/BSA policy or the Royal Australian and New Zealand College of Radiologists (RANZCR) and New Zealand does not align with other commonwealth countries in endeavouring to optimise our screening programme. The emphasis in the BSA Review Epidemiology Report on the difficulty of implementation of a number of initiatives along with disproportionate concern regarding over-diagnosis is disappointing and warrants deeper discussion. The initiatives aim to identify and stratify people according to risk, thus reducing both under-diagnosis and over-diagnosis. As consumers we are concerned that in New Zealand, despite international evidence, the balance of concern is tipped toward over-diagnosis. We welcome a more balanced approach in the review of new evidence with **greater consideration of the impacts of under-diagnosis**.

1. **Objectives of our Screening Programme**. The current focus in both the BSA Review Report and the associated Epidemiology Report is on mortality. We believe we should bring an **emphasis to interval cancers, late stage/high-grade diagnoses and de novo/advanced diagnoses as lead indicators for the screening programme**. Mortality should remain an important focus, but it is a lag indicator. This suggestion is well supported by current evidence, locally and globally. In addition, some emphasis on quality of life and cost impacts across the health system is needed. There is a cost to the system when comprehensive treatment is required for long periods of time following late-stage higher grade, de novo or advanced diagnosis. We need to aim to reduce these impacts and costs. Greater investment is needed at the front end of the system by incorporating risk stratification alongside screening when considering extending the screening age range, using differing screening modalities or frequency. These inputs can be modelled utilising health economics and GIS together with data from the Breast Cancer Register and other sources.
2. **Research integrated into our screening programmes.** Approaches to optimise the breast screen system need to be multifactorial e.g., how invites occur, entry and exit, timing of invites, appeal to different audiences, how accessible the system is, a holistic approach which has a risk focus, frequency between screens, modality of screening for differing risk profiles, rescreening follow-up and management of abnormal screens and lastly re-entry. By incorporating research and learning as an integral part of the breast screen pathway, opportunities for improvement would be tailored to our population. We currently do not seem to have the capacity to achieve this as the breast cancer pathway awaits progress in Lung, Bowel and HPV. When optimisation of screening programmes with an objective of mortality reduction is delayed we are impacting lives and whānau.
3. **Modality:** Both BSA Review reports are for all intents and purposes silent on modality. The options now available and the flexibility they may provide in outcomes and cost effectiveness, is a weakness of the report. No one modality can provide the answer, it is how we fine tune and optimise systems with the whole picture in mind. For example, there could be an ultrasound or Contrast Enhanced mammography (CEM) system on a screening bus that visits remote locations so that those being screened, needing a rescreen or needing follow up could have access without the need for a visit to a distant hospital. This would be beneficial to the health system as a whole. The sensitivity and specificity of these systems is detailed on the following link. In broad terms a mammogram costs $150 -$350 (tomosynthesis), an ultrasound $200-400 a CEM costs below $600 and an Abbreviated MRI $700-800 (now closer to $1500) and full MRI $2000 approximately. Specificity accrues from 5-7/1000-16.5/1000 across the spectrum. https://densebreast-info.org/screening-technologies/cancer-detection-by-screening-method/

Conclusion

There is strong evidence that simply stratifying our population as at average and high risk is inadequate particularly as we are not taking all risk factors into account e.g., high breast density.

The BSA Review has identified a potential starting point to achieve improvement with a focus on equity. We agree with this priority but suggest concurrently we also need a longer-term vision for our screened and symptomatic pathways beyond arbitrary measures and assumptions. Should we be stratifying low, average, moderate and high-risk participants based on the latest evidence and if so where does responsibility lie given that moderate risk participants are currently not being assisted through the high-risk pathway. These people receive a letter from Genetic Health Service NZ and are asked to be proactive. Some will, some won't. This is not the road to equity.

Mammographic density (MD) reflects cumulative exposure to reproductive and other life events with a hereditary underlay. It is now considered to be a biomarker of risk and is changing how we screen alongside other risk factors. Consumers have a right to know about breast density. They are now increasingly health literate and aware. We welcome the recognition within the BSA Review reports of the voice of the consumer in how we deliver improved health outcomes. We seek to be heard.

Digital Mammography is providing an ability to more reliably look into the future which has major implications regarding risk and screening programmes and their success. Other countries may not all have optimal screening pathways, with the possible exception of Sweden. The important point is that New Zealand is not progressing while other countries are. Our unique population deserves better. AI may prove a powerful option for New Zealand to facilitate progress as we strive to do better.

We need to diagnose earlier to reduce the risk of advanced cancers and to reduce mortality.

Multifactorial risks such as mammographic density and genetics alongside other risk factors is shifting our view of population screening and this is now being translated into practice, including prevention.

Clinical care needs to change with the information now available, key stakeholders need to work together to establish clearer pathways because people are losing faith in the quality of screening given the refusal to tailor services when new evidence presents.

The RANZCR position statement on density is problematic [53]. We need more leadership from both radiologists and surgeons. Their resistance may come from a combination of lack of capacity and or clarity on what a new clinical pathway may look like and limited opportunities for improvement. It may also come from being overly conscious of cost without thinking through costs to the broader health system and society. It would be very refreshing to have a discussion with this group. What we do know is that those who can afford to access private services are doing so and this does not improve equity of outcome for all.

The College reporting guidelines for mammography recommend that breast density be listed in the mammogram report. They go on to say this is not implemented in the BreastScreen programmes in Australia or New Zealand, where a formal report is not issued.

In addition, some emphasis on quality of life and cost impacts across the health system is important.

There is a cost to the system when comprehensive treatment is required over long periods of time following late-stage higher grade, de novo or advanced diagnosis. We need to aim to reduce these impacts and costs.

Role of Artificial Intelligence: prospective and retrospective initiatives

Rebooting cancer screening with artificial intelligence

Adams and Topol discuss the incorporation of artificial intelligence (AI) into cancer screening in The Lancet (2023) [54] as follows:
Cancer screening typically relies on an all-comer population approach, with screening eligibility based predominantly on age. This approach does not account for the multidimensional complexity of each individual, including a person's biological, physiological, and environmental data, and can miss those who may be at high risk of disease. As the total number of cancer cases continues to increase, and at younger ages, a rebooting of cancer screening is needed.

In the future novel types of data at the individual level and the ability to analyse them with artificial intelligence (AI) models have the potential to make cancer screening more efficient and cost-effective. New data inputs, such as genome sequencing, circulating cell-free tumour DNA (cfDNA), combined with medical imaging and AI models, could provide clinically actionable outputs from complex data.

The cost for whole-genome sequencing has reduced, and population sequencing of specific risk genes, such as for hereditary breast cancer syndrome and Lynch syndrome, has been shown to be cost-effective. Additionally, polygenic risk scores can provide independent and additive data for risk determination and might in future enable screening programmes to extend to new age ranges and cancer types.

Beyond the new data inputs is the potential to extract far more information from routinely obtained images including, mammograms that contain a wealth of data, much of which is **beyond human perception.** Analysing these sources of health data with **new AI models presents an opportunity to improve risk stratification and make early disease detection strategies more accurate and efficient.**

New data inputs and the ability for "machine eyes" to see what is not perceptible to humans points towards a potential transformation for cancer screening. AI analysis of multimodal data sources could give rise to a statistical biopsy, offering a comprehensive, personalised approach to screening and early cancer detection.

Development of AI models to efficiently integrate an increasing number of data sources and the validation of AI models in diverse populations is needed. **Health-care systems need to harness a shift towards more informative screening to improve efficiency and cost-effectiveness—with improved accuracy and outcomes at the individual and population levels.**

AI and breast cancer and randomised prospective trials

The role of AI in breast screening as detailed in a recently reported interim analysis concludes: "AI-supported mammography screening resulted in a similar cancer detection rate compared with standard double reading, with a substantially lower screen-reading workload, indicating that the use of AI in mammography screening is safe." Lang et al. reported in The Lancet Oncology, August 2023 [55]. Thus, the use of artificial intelligence in breast cancer screening **has not only been demonstrated**

to be safe but can also almost halve the workload of radiologists. The trial described by Lang et al. was the first reported randomised controlled trial of its kind involving more than 80,000 women. Results also suggest **AI screening does not increase false positives** as well as almost **halving the workload**.

Previous studies examining whether AI can accurately diagnose breast cancer in mammograms were carried out retrospectively, assessing scans that had been looked at by clinicians. A study that followed women from Sweden with an average age of 54, compared AI-supported screening directly with standard care. Half of the scans were assessed by two radiologists, while the other half were assessed by AI-supported screening followed by interpretation by one or two radiologists. In total, 244 women (28%) recalled from AI-supported screening were found to have cancer compared with 203 women (25%) recalled from standard screening. This resulted in 41 more cancers being detected with the support of AI, of which 19 were invasive and 22 were in situ cancers.

There were 36,886 fewer screen readings by radiologists in the AI group compared with the group receiving standard care, **resulting in a 44% reduction in the screen-reading workload of radiologists**.

The final results of the trial will report interval cancers in 100,000 enrolled participants and will demonstrate whether AI can reduce the number of interval cancers – cases detected between screenings that generally have a poorer prognosis – and whether the use of AI in screening is justified. The lead author, Dr Kristina Lång, from Lund University in Sweden, said, "We still need to understand the implications on patients' outcomes, especially whether combining radiologists' expertise with AI can help detect interval cancers that are often missed by traditional screening, as well as the cost-effectiveness of the technology although it is expected waiting times for patients would reduce."

A second prospective study from Sweden, just published (Karin Dembrower et al, September 2023 [13]) which included 55,581 women between the ages of 40 and 74 undergoing regular screening also found that **replacing one radiologist with AI resulted in a 4% higher diagnosis for cancer detection rate compared to radiologist double reading demonstrating that AI within a screening clinic setting has potential for controlled implementation that includes risk management and real world follow up.** The added value from this study was that it also demonstrated that **single reading by AI compared to double reading by two radiologists was also non inferior along with the benefit of integrating AI into existing screening workflows.**

These prospective findings are important because current risk assessment models require collection of detailed patient specific clinical and family history which can be prone to omissions. They also tend to estimate lifetime risk at the population level and fail to estimate risk for an interval cancer. Trials such as MyPeBS and WISDOM are using these clinical risk models to optimise screening intervals however such models are perceived as challenging to incorporate into screening and primary care and are not generalisable to the general population as they are developed on homogenous populations or in those carrying genetic predispositions. **Importantly, spontaneous cancers do develop in patients not known to have any risk factors i.e., randomly and therefore these deep learnings will reduce diagnosis of advanced stage disease and breast cancer mortality in women of average or intermediate risk.**

The recent advances in imaging technology and artificial intelligence (AI) deep learning risk models are showing significant promise in substantially improving the accuracy of personalised risk assessment. Multiple studies have now shown that high breast density, more complex mammographic tissue patterns, high glandular volume on ultrasound images and marked

background parenchymal enhancement on MRI scans are associated with or linked with increased lifetime risk.

In addition, research has demonstrated marked variability among radiologists' reading accuracy, there is a global shortage of radiologists (also impacting New Zealand) and there are increasing demands for greater precision from providers and patients. The benefit of being more precise may also mean that we can focus greater attention where it is due.

The UK has also reported on its review of AI following a stakeholder meeting with delegates from Denmark, Netherlands, Norway, South Korea, Sweden, and USA as highlighted by country pp.13-18. This meeting has acknowledged and concluded that breast cancer screening programmes are likely to change in the next few years in mammography reading strategy, because previous retrospective studies have demonstrated at least non-inferior performance when using an AI algorithm[12]. Several strategies have been proposed to adapt mammographic screening, including AI serving as one of the two readers, AI selecting cases to be single or double read, and AI selecting cases to be recalled.

The UK National Screening Committee highlighted the key areas where evidence is required to measure the effect of implementation of AI algorithms within the NHSBSP. The stakeholders are of the view that a **multicentre multivendor testing platform with opt-out consent** is required and a service evaluation was preferred to a full randomised controlled trial. Automatic recall of cases using an agreed high sensitivity AI score versus automatic rule out with a low AI score set at a high sensitivity could be used. **A human reader should still be involved in decision making with AI-only recalls requiring human arbitration**. Standalone AI algorithms used without prompting maintain unbiased screen reading performance, but reading with prompts should be tested prospectively and ideally provided for arbitration. Their analysis highlighted AI activity globally.

The following table highlights ongoing prospective trials.

Overview of ongoing prospective trials on AI algorithms in mammography screening.

Trial name (ID)	Study design	Country	Principal Investigator	Number of participants	AI vendor	AI strategy
n/a*	Clinical evaluation	Denmark	I. Vejborg	n/a*	Transpara (Screenpoint Medical)	AI score determines number of readers: score 1–5 = SR, score 6–10 = DR score > 9.98 = recall by AI
PRAIM (DRKS00027322)	Observational	Germany	A. Katalinic	400,000	Vara	DR versus SR + AI
AI-STREAM (NCT05024591)	Observational	South Korea	Y. Chang	32,714	Lunit	SR versus SR + AI
AITIC (NCT04949776)	Observational	Spain	E. Cabot	27,000	Transpara	AI score determines number of readers: Score < 8: none Score > 7: DR + AI assist
MASAI (NCT04838756)	RCT	Sweden	K. Lång	100,000	Transpara	DR versus SR + AI
ScreenTrusCAD (NCT04778670)	Observational	Sweden	F. Strand	55,579	Lunit	DR versus SR + AI versus independent AI
AI-ROL (NCT05048095)	Observational	Sweden	H. Gustafsson	15,500	Transpara	DR + AI Cases not recalled by DR but 3 % most suspicious AI score: recall by AI
GEMINI (NHSX phase 3)	Prospective	United Kingdom	G. Lip	200,000	Kheiron	DR with AI in background
Service evaluation (NHSC phase 4)	Observational	United Kingdom	Various PI's	Unknown	Kheiron	AI in silent background
AIMS	Prospective	United Kingdom	A. Darzi	Unknown	Google	AI in silent background

Abbreviations: *ID* identification number, *AI* artificial intelligence, *n/a* = not applicable, *RCT* randomized controlled trial, *DR* double reading, *SR* single reading, *Transpara score 1–5* = 50 % of cases with relatively low risk breast cancer score, *Transpara score 6–10* = 50 % of cases with relatively high risk breast cancer score.
* AI already incorporated in nationwide breast cancer screening.

Source: van Nijnatten, Payne N.R. et al. 2023. Overview of trials on artificial intelligence algorithms in breast cancer screening - A roadmap for international evaluation and implementation. https://doi.org/10.1016/j.ejrad.2023.111087

While these prospective studies are very timely and are being described as a tipping point for AI in breast screening, retrospective trials will continue to provide new knowledge.

Retrospective trials

Retrospective evidence continues to increase, and there have been improvements in the size and quality of data used for evaluation. Overall, they have a place in the evaluation pathway of AI, enabling scientists to test various applications, using different commercial and academic algorithms, on different cohorts of patients as well as identifying the appropriate threshold for use. Thus, retrospective studies provide a framework for prospective work and guided programme adoption [12].

For example, a recently reported Danish study, Lueratzen et al, 2023 [56] demonstrated that by combining a diagnostic AI system with a mammographic texture model it was possible to achieve **improved risk assessment for interval cancers and long-term cancers and enabled identification at high risk. Risk tools such as this enable quick risk assessment relative to those relying on questionnaires and this study demonstrates that mammographically based deep -learning models estimate risk robustly and objectively without the need for questionnaires and genetic work up and may be better suited to breast screening practices.** Diagnostic models identify short term risk and are trained to detect suspicious lesions and to support diagnostic assessment. **Texture models are trained to learn global features in healthy tissue indicative of breast cancer tissue, heterogeneity, density or both for long term risk.** This Danish model identified women with 10% combined highest risk accounting for 44% of interval cancers and 33.7% of long-term cancers with 90% specificity but lower sensitivity at 36.5%. Area under the receiver operating characteristic curve (AUC), a measure of sensitivity and specificity describing the inherent validity of the test, was 0.72.

Artificial Intelligence Risk Model (Mirai) was validated on breast screening data sets from 7 different countries. From a total of nearly 129,000 mammograms taken from over 62,000 patients that detected 3,815 cancers, Mirai obtained concordance indices (AUCs) of between 0.75 and 0.82 across the seven sites for cancers detected within 5 years of screening [71]. This compares favourably with an AUC of 0.62 from traditional risk models such as Tyler-Cuzick.

Observational clinical trials such as Wisdom have identified a new biomarker of risk through an association of Background Parenchymal Enhancement (BPE) suggesting when MRI is used (it can only be detected on MRI) BPE is recognised as a risk factor alongside breast density [57].

Fay Sowerby's response to BreastScreen Aotearoa's draft review and epidemiology reports highlighted the following regarding AI:

Artificial Intelligence: The BSA Review reports are silent on AI. AI programmes are providing new detail on how mammograms can provide valuable information to understand risk prior to the next screen, as detailed below and for that reason AI should have been included.

Personalised approach: In Australia Dr Helen Frazer Radiologist, Breast Cancer Screening Clinician, AI Researcher, ANZ Women in AI Innovator of the Year (2022) and Epidemiologist, sees screening as a successful public health initiative. The BRAIx project in Victoria Australia is seeking to understand if an AI reader can enable a new personalised screening model (segmenting by age, family history, density) to predict future risk. Utilising a retrospective data set (2014-19) to evaluate true negatives (normal and no interval cancer), false negatives (interval cancers), false positives (assessed normal and no interval cancer), and true positives (screen detected cancer). Using AI, through 2016/17 they saw a recall reduction of 16.1%, a 1.4% reduction in interval cancers and a 19.7% reduction in

reading and assessment costs. They have now moved into real world evaluations. She quotes Hippocrates "declare the past, diagnose the present and foretell the future" [58].

Reduction in false positives and workload: Mads Neilson, Professor Image Analysis, Computational Modelling and Geometry, University of Copenhagen, Denmark, rolled out an AI programme in Denmark that showed comparable sensitivity and higher specificity than radiologist alone. A 63% reduction in radiologist workload and a 25% reduction in false positives was achieved. This programme was driven by being unable to screen everyone within the required interval, a shortage of radiologists and concerns regarding quality and cost. This approach helped identification of mammograms in less urgent need of a double reading and reduced recall rates by 17% [56].

"Average risk" women can be at substantial risk of breast cancer: John Hopper, Australian genetic epidemiologist and professor at the University of Melbourne, Australia, reviewed several AI programmes and suggested that AI algorithms to detect breast cancer provide information on future risk in the short term. This work, he suggested, reveals women otherwise considered cancer free at screening, but at substantial risk of breast cancer in the short term. This raises the issue of joint decision making. Hopper notes the need for considerable care in implementation (https://www.mybrisk.org.au/launch-of-cre/).

Prevention and Risk Stratification within screening interval: Michael Eriksson, Department of Medical Epidemiology and Biostatistics , Karolinska Institutet Sweden and team use the AI programme KARMA in breast screening. KARMA provides information on long term performance of an image based short term risk model for breast cancer (https://karmastudy.org/about/) [59]. They see a role for KARMA in prevention (lifestyle, prophylactic medication), ability to assess risk across 10 years, and personalised screening to reduce late stage and higher-grade diagnoses. Short term risk identifies women likely to develop breast cancer after the current but before the next screening visit. The short-term risk tool provides a clinically actionable window to inform a clinical decision at the time of current screening. Eriksson stated that 30-50% of cancer can be prevented. Not all women have a high-risk breast cancer, you need to look out to 10-year risk to identify women early. High risk women can be offered risk reducing options such as lifestyle change and medical interventions. The Karolinska team have developed three AI models. Model 1 is based on age and image features only; Model 2 is based on family history and lifestyle factors and Model 3 adds genetic determinants. For the study reported they utilised Model 1 and validated it against Tyrer-Cuzick. The KARMA risk model outperformed Tyrer-Cuzick for a 10-year view. The AUCs for KARMA ranged from 0.76 to 0.66 over 1-10 years. While Tyrer-Cuzick ranged from 0.67-0.62. KARMA is a model that is clinically useful in identifying women who will benefit from intervention. This model is not technology dependent.

Determining Future Risk, Stratification and modality selection: Per Hall, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Sweden. Individualised prevention and screening of breast cancer: the KARMA experience https://staff.ki.se/people/per-hall [60]. The purpose of a mammogram is to detect cancer but there is information in a mammogram that can determine the future risk of breast cancer. Parity, age at first birth, breast feeding, density, use of HRT can be added to the model. These features are intuitive to radiologists. AI helps you know whether a second reader is needed. For those at risk it also helps to identify false negatives. Hall et al. recommend using tomosynthesis for breast AI models i.e., 2-300 images and not 4, along with the use of longitudinal risk estimates. Discrimination reached over 0.82. They broke their population into low (45%), general (31%), moderate (11%), high (8.6%) and very high (5.4%) risk, with differing risk ratios from 1 for low to 25 for very high. Interval cancers can be predetermined at each % of risk (Eriksson, 2020). Those at low risk have the option of no screening, those at general risk are screened according to screening programme and those at high and very high have intensified screening and

supplemental screening and are offered preventative measures. The team recommends that arbitrary cut offs for risk models are not helpful and it is better to assess risk over the interval screening period. The next step is seen as modelling longitudinal information which is what radiologists do.

These findings suggest that stratifying our population as at average risk and high risk is inadequate. They also suggest we need to boost our symptomatic pathways and better stratify risk, given that **the Karolinska team stress screening pathways should not be arbitrary.**

Prediction of interval cancers and invasive cancers: Celeste Damiani, Queen Mary Hospital London is adopting and implementing the MIT model (MIRAI) in a medical facility in London. This model is technology dependent (HOLOGIC) and does include breast density. MIRAI 3-year risk was associated with future interval and screen detected cancers and was a stronger predictor of interval than screen detected cancers. The model was slightly more predictive for invasive than in situ cancer. Seen as a predictor of 3–6-year risk, with accuracy high at 0.70 for HR+ breast cancers [61].

There is no doubt that **Sweden is successfully using mammography and tomosynthesis-driven AI to assess risk and find cancers earlier, with more precision and improvements in productivity. Their interval cancer rate was low.**

Māori health equity / Te Tiriti obligations

A document entitled 'Te Tiriti o Waitangi and the National Screening Unit (NSU) Statements of Intent' (dated October 2022) makes clear that NSU has moved to align the work of the NSU with the principles of Te Tiriti o Waitangi and Māori Data Sovereignty. A Māori Public Health Register has led this work, a series of wānanga; and the commissioning of the Māori Monitoring and Equity Group (MMEG) to provide options for aligning the Governance of the NSU with the Principles of Te Tiriti o Waitangi. These incorporate **Development of a Māori Reference Group** to guide the development of a Te Tiriti Governance Partnership Model with commitments towards achieving equity for Māori in national screening programmes in Aotearoa. Collectively, the group discussed a commitment to work together to achieve the shared vision of people and whānau benefitting from high quality, equitable and mana-enhancing national screening programmes.

The NSU is committed to a co-governance approach knowing it is essential to achieving equity a mandate to uphold the principles of Te Tiriti o Waitangi. The shared vision is 'People and their whānau benefit from high quality, equitable and mana-enhancing national screening programmes.'

The NSU commits to these principles:

Tino rangatiratanga

Provide for Māori self-determination and mana motuhake in the design, delivery and monitoring of health and disability services.

Equity

Being committed to achieving equitable health outcomes for Māori.

Active protection

Acting, to the fullest extent practicable, to achieve equitable health outcomes for Māori. This includes ensuring that the Crown, its agents, and its Treaty partner under Te Tiriti o Waitangi are well informed on the extent and nature, of both Māori health outcomes and efforts to achieve Māori health equity.

Options

Providing for and properly resourcing kaupapa Māori health and disability services. Furthermore, the Crown is obliged to ensure that all health and disability services are provided in a culturally appropriate way that recognises and supports the expression of hauora Māori models of care.

Partnership

Working in partnership with Māori in the governance, design, delivery and monitoring of health and disability services – Māori must be co-designers, with the Crown, of the primary health system for Māori.

We as consumer stakeholders are uncertain where measuring and reporting density sits within NSU/BSA's/Te Tiriti partnership timelines as a priority, but we suggest that detecting cancer early will reduce the burden of cancer on whānau and communities. Addressing this issue should go some way to reducing inequities that are currently developing through a two-tier system, i.e. private vs public.

In reading the intent document it appears that the opportunity for improvement will best be managed by Māori in their communities when policy and protocols have been developed on a co-governance basis. This level of oversight and partnership we would hope will ease the pathway for measuring and reporting density once the partners have agreed that this will likely assist in reducing inequity, given those seeking privately funded care are currently receiving this information and in many instances supplemental screening.

In addition, we query whether withholding and not reporting breast density data is against data sovereignty principles within the Intent. For example, access to one's own health information is covered by Rule 6 of the Health Information Privacy Code 2020 and S 22F of the Health Act 1956. In addition, Right 6(1) of the Code of Health and Disability Services Consumers' Rights 1996, promulgated under the Health and Disability Commissioner Act 1994, gives patients the "right to information that a reasonable consumer, in that consumer's circumstances, would expect to receive", including the results of procedures or tests.

Under Te Tiriti o Waitangi, the New Zealand government must protect the rights, interests and taonga of Māori people. Special considerations arise from a Te Ao Māori perspective, which existing laws (focused on individual entitlements) are inadequate to protect:

(a) health information is regarded as a taonga that must be cared for, used and treated with respect; and

(b) genetic information is viewed as collective (rather than individual) property, since it carries information about whānau, hapū and iwi (both historical and current/predictive).

These are important discussions that need to be had regarding risk stratification, age extension and breast density notification, alongside other discussions relating to access and participation.

BCAC's view is that **we can no longer leave women including Māori, Pacific, Asian and other high-risk women "blind" to breast density**.

Addressing concerns regarding potential harms of reporting breast density

Empowering Women to Confront Dense Breast Concerns and to work with health professionals regarding their care.

In our view as consumers **women are willing and able to deal with any psychological issues** relating to breast density in their efforts to reduce their risk of a late-stage breast cancer diagnosis.

"If you can show, by measuring and reporting density, that you are finding more cancers, fewer cancers are being diagnosed between screening rounds, and the stage, the size and the nodal status of cancers that are diagnosed is moving in a favourable direction, I believe that's sufficient to encourage implementation with a planned review in 10 years when the mortality information's there." Professor Bruce Mann, Road Map to Optimising Screening ion Australia (ROSA) [47].

Prof Mann further emphasises "As women and the community become more informed, there is a danger that what is offered by BreastScreen will be seen as insufficient, which will lead to women opting out of BreastScreen and going private. What we don't want in this country is a two-tiered system where those who know and can get the best, do, and everyone else gets what's offered to them. That's what we are working to avoid."

There has been considerable comment on potential harms and over-reporting from the inception of mammographic screening. To correct perceptions that had developed and been reinforced over many years the ROSA team published research in 2021 showing that **the rate of overdiagnosis has likely been overestimated** in the past with a finding that "**overdiagnosis accounts for less than 10 percent of invasive breast cancer cases among women ages 50 to 69. Estimates above this level are likely to derive from inaccuracies in study design**…. The detection of breast cancer before symptoms arise greatly increases the chance of prolonging survival or even curing malignancy…. The findings reaffirm the idea that observational studies require careful design to avoid methodological pitfalls and highlight the value of insight gained from well-calibrated modelling studies. " There is therefore a clear need to keep a firm emphasis on preventing harm while safely minimising over diagnosis [62].

Ritse Mann et al. [3] noted that underdiagnosis is more of a problem in women with extremely dense breast tissue compared to other women. In women with largely fatty breasts, the sensitivity of mammography screening is 86 to 89%, meaning that only 11 to 14% of cancers present as interval cancer between two screening rounds. This sensitivity decreases to 62–68% in women with extremely dense breasts. For full-field digital mammography (FFDM) similar poor figures were reported, with a program sensitivity of only 61% based on biannual screening.

A false positive or a false alarm: When a screen finding is abnormal further assessment is required to establish a diagnosis and to decide whether cancer is present or not. **Where this assessment confirms the presence of breast cancer, the respective screening finding is considered a 'true-positive'**; **when the assessment proves the presence of a benign change, but no breast cancer, the respective screening finding is considered 'false positive'**—possibly better understood when referred to as **'false alarm'**.

Women should be informed that supplemental screening tests in general will increase the chance they will at least once experience the situation of a 'false alarm', i.e., receive a positive screening test which, after appropriate assessment, turns out to be a harmless finding.

Women should also be informed about the fact that the 'assessment' to find out whether a positive screening finding corresponds to cancer or not will consist of some additional imaging studies for most, and/or of minimally invasive vacuum needle biopsy. The latter is regarded as unpleasant and somewhat painful, yet generally is a well-accepted procedure [63].

Where the assessment confirms the absence of breast cancer, women may have experienced an (eventually unnecessary) fear of having breast cancer for a few days until the assessment results are available. In this instance we request that effort should go into keeping the time to the final diagnosis short.

In contrast, a false negative result or a late diagnosis will be life-changing, lead to avoidable surgery, chemotherapy and radiotherapy as well as physical, mental and often financial stress on the person diagnosed and their whānau and may inevitably be fatal.

We as consumers stress that no woman should ever be treated for breast cancer because of a false-positive screening or a "false alarm" finding. Only when pathologic review shows cancerous tissue should women receive treatment. Accurate pathological procedures are an essential component of diagnosis.

Overdiagnosis

Some cancers detected during screening may never have become symptomatic before the affected woman would have died of other causes. Diagnosis of such cancers is referred to as 'overdiagnosis'. **In reality, overdiagnosis is not knowable at the individual level at the time of cancer detection. In practice, these women will generally be treated for their disease as currently there is no reliable method to determine whether a specific cancer is life-threatening or represents an 'overdiagnosis'.** Based on the modelled DENSE data, about 25% of mammographically detected cancers (in 1.7% of women) and about 22% of MRI detected cancers (in 2.1% of women) may represent overdiagnosis [31]. These are **mainly the low grade in situ**, and some **very indolent invasive breast cancers**. Treatment is tailored to the specific biology of the disease in any given patient. Therefore, while overdiagnosis cannot be prevented, the effect is mitigated by adapting the treatment to the aggressiveness of the detected cancer.

Population based screening has always focused on the substantial benefit for the few from engagement by the many. There are now 4,500 diagnosed with breast cancer in New Zealand each year, and 25 men along with 700 who will die of breast cancer. There is a lifetime risk of getting breast cancer for women in the general population of one in nine. Of the 4500 only 2600 were in the screening age range. (Mr Adam Stewart, Clinical Director BSA, presentation, BreastSIG, October 2023). It is also worth reflecting that of all invasive cancers in women in the screening eligible age groups, about 45% are detected on screening, the remaining 55% are detected symptomatically and 18% are interval cancers in women. [74]

For some women, this proportion may lead them to conclude they can avoid screening. It is important to consider whether, if they were informed, they had high breast density, they might be more committed participants. They may then wish to avoid a false negative rather than a false positive.

We as consumers see a need for more information to be provided to women to better enable informed shared decision making and self-determination. Decisions will be made within the context of each woman's individual preferences and values, the hallmark of informed decision-making.

We believe we have moved from an era when experts could simply advise people what to do to one where good information must be provided to allow good decisions. This participatory process is essential in informed consent. There is also an obligation to offer techniques that are proven effective, otherwise freedom of choice is denied. It is at this level that participation rates in a screening programme and personal choice may clash. The concept of informed decision-making drives our thinking away from a One Size Fits All model in which we are all treated as if we have average risk. Newer evidence has shown that one size does not fit all, and in our view that approach is causing harm to those who are not average including those outside the screening age range.

To underscore the importance of earlier diagnosis, we share on page 36 over, details from a study recently published entitled True Cost of Breast Cancer, Wilkinson et al, 2023 [64]. This study investigated the costs of breast cancer by subtype and stage. It clearly demonstrates there are significant benefits to be gained from screening and early diagnosis versus the cost of late-stage diagnosis. This study found that the often-quoted figures have increased and should now be regarded on a cost per case basis for DCIS NZ$15,564, Stage 1 NZ$42,031, Stage 2 NZ$82,725, rising to Stage 3 NZ$105,695 and NZ$400,318 for Stage 4.

This tells us that the cost of screening whether that be MRI or ABBMRI, CEM, Ultrasound or Mammography may be regarded as a worthwhile investment to avoid not only the suffering but also the costs of a late-stage diagnosis.

In comparison Waka Kotahi recently established a new Value of Saving a Life (VoSL) figure of $12.5M based on a robust survey of 8,000 New Zealanders, conducted in 2020/21 based on similar studies in other countries. Lincoln Universities, Denne & Kerr and Infometrics Chief Economist Dr Adolf Stroombergen asked respondents to put a value on avoiding a minor or serious injury or avoiding gridlock every day. It is worth highlighting that almost twice the number of New Zealanders die from breast cancer each year than from the road toll. There is much to be gained from investing in earlier diagnosis for individuals and their whanau. [75]

If we are to avoid impacts on quality of life for individuals and their whānau and the financial cost to the health system and often to individuals who may need to fund their own treatment, then we need to measure, report and inform women of their breast density to more effectively avoid late-stage diagnosis for these women and impacts on their whānau. Figure 3 below differentiates these issues by subtype.

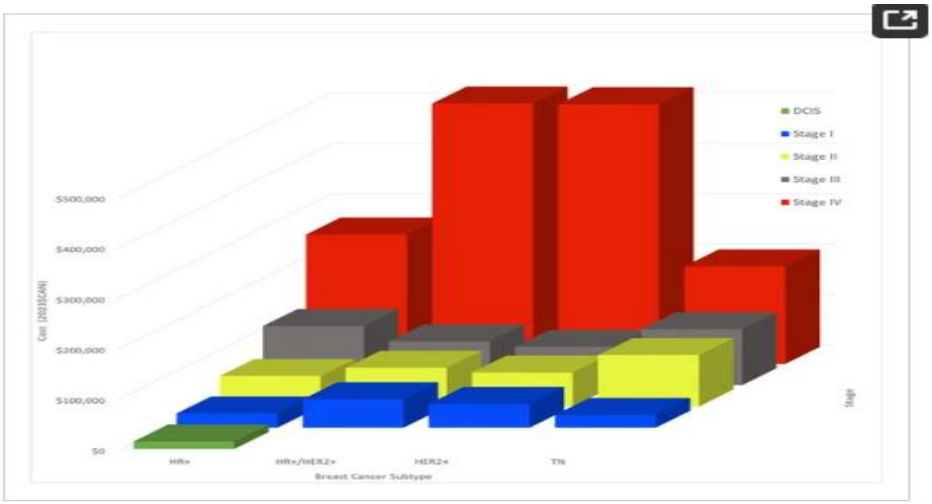


Figure 3. Breast cancer per-case cost in C$ of treatment by stage and molecular subtype.

Source: Wilkinson, A.N.; Seely, J.M. et al. Capturing the True Cost of Breast Cancer Treatment: Molecular Subtype and Stage-Specific per-Case Activity-Based Costing. *Curr. Oncol.* **2023**, *30*, 7860-7873. https://doi.org/10.3390/curroncol30090571

As is often said, mammograms continue to be the gold standard in screening for early detection of breast cancer and determining whether a woman has dense breast tissue.

Now, through prospective studies we can add to that claim that mammograms can also be regarded as a very efficient and valuable risk stratification tool allowing breast cancer to be predicted and detected in the short and longer term [13,55]. Reports vary regarding the number of women who will have dense breast tissue, but it is reported by The National Cancer Institute as 50% for those 40 years and older and 40% for Category C and D densities by BreastScreen South Australia, making it quite common among women.

Recent research has shown most women are unaware of the fact they have dense breast tissue or the possible impact it may have on their health. There are many women however who have been diagnosed late stage or de novo who have been very vigilant about their screening. That group of women are now very well informed as well as being rightfully angry and dismayed that their cancer was not detected earlier, when potentially curable i.e. less likely to recurr.

Although the challenges associated with dense breast tissue and mammograms are recognised, experts in the field struggle to agree on what other screening tests, if any, should be undertaken in addition to mammograms for women with dense breasts. The NCCN guidelines are the most practical and yet well evidenced and are without provider, country or regional influences [35].

Breast cancer advocates all agree that all women should be informed if they have dense breast tissue because it is well established that breast density diminishes mammography's ability to detect breast cancer, potentially resulting in a negative mammogram that may provide **false reassurance**. If a patient's mammogram report states that they have dense breast tissue, it is important they are told the significance of this and recommended to speak to their GP or radiologist to discuss further testing along with any other health or genetic factors that may increase their risk for breast cancer.

BCAC's view is that providing patient access to information in their mammography reports is an essential component of a comprehensive breast health strategy. Such an approach allows informed decision making and should certainly not be regarded as over-reporting.

To support a move to openness and education, the FDA on March 9, 2023, announced updates to the mammography regulations under the Mammography Quality Standards Act of 1992, a law passed to ensure quality mammography. This now **requires all US mammography facilities nationwide to notify patients about the density of their breasts**. The amendments provide specific language explaining how breast density can influence the accuracy of mammography. The new rules mandate that providers include an assessment of patients' breast density in mammogram reports to inform them about the potential limitations of their screenings and enable them to make informed decisions about further testing.

The new amendments will enhance the FDA's ability to communicate directly with patients if facilities do not meet the quality standards. Patients receiving personalised information about their breasts will be more knowledgeable and aware of additional steps to take to ensure breast cancer does not go undetected.

The FDA's recent announcement is aimed at empowering women and clearly concur with BCAC's view that women should be informed so they and their whānau can be proactive in protecting their breast health. Women and their whānau should be encouraged to engage and communicate with their health service providers to make informed decisions about additional screening, if needed.

We welcome BreastScreen Aotearoa's recent aspiration to achieve early diagnosis and to reduce morbidity alongside mortality. Informing women of the risks of breast cancer and the need to be screened but failing to inform them of their breast density once screened, will continue to result in false negatives, interval cancers and late diagnoses. This needs to be redressed. The rationale is simple, those with high density are not at average risk.

BCAC as members of Aotearoa NZ Breast Cancer Communities Private Facebook Group which offers peer support for those recently diagnosed, we learn of others experience. In October the issue of Breast Density was frequently mentioned. Most recently it related to the challenge of having an interval cancer recognised as a treatment injury from misdiagnosis. Some specialists refrain/resist from signing the ACC 2152 and ACC 45 form. This resistance relates to not wanting to be seen to be criticising NSU/BSA or to cause concern for a provider. Interval cancers are a product of a system which does not measure nor report breast density, they are not the fault of a women or a provider.

Ultimately, informed New Zealand consumers wish to see a move to tailored screening for those who are not of average risk. Screening which takes into consideration a patient's mammographic breast density along with other lifetime breast cancer risks, to guide breast cancer screening strategies that are more individualised and comprehensive. For the purposes of this submission, we are only addressing the need to measure and report breast density.

Supplemental Screening

While there is no single guideline uniformly recommending annual supplemental screening based on dense breasts alone, women with a combination of risk factors may expect to have an estimated lifetime risk of ≥20% and therefore in the US and Europe are likely to meet high risk screening guidelines as highlighted in Appendix 2 and references 73 and 74. These detail NCCN, American Cancer Society (ACS) and the American College of Radiology (ACR) guidelines including the updated recommendations for higher-than-average risk and the appropriateness criteria for women with dense breasts and the European Society of Breast Imaging.

Women with dense breasts should have routine screening mammography using 3D mammograms (Tomosynthesis) because of its slightly improved cancer detection, improved specificity and reduced late-stage disease. In New Zealand the decision to offer supplemental screening beyond mammography is up to the provider and will significantly depend on where a person resides and will be reliant on a referrer. The most frequently used guideline in New Zealand is eviQ which does not recognise breast density, instead focussing on family history and a range of other criteria.

As a consumer organisation we see the need to inform women if they are above average risk. We enable this for familial and genetic conditions, and we are intrigued why breast density either alone or in combination with other risk factors would be treated differently. Even without performing formal risk assessment, imaging guidelines can help identify women who will meet criteria for supplemental screening.

Research supports the effectiveness of MRI and Abbreviated MRI for women with dense breasts. Based on the DENSE trial we know the EUSOBI recommendations suggest every 2 to 4 years in women aged 50-70 as highly cost effective. [73]

For women with a personal history of breast cancer and a diagnosis by age 50, dense breasts or both, the ACR recommends supplemental screening with MRI. [73]

Annual screening MRI is recommended in high-risk women to begin at 25-30 years of age. This includes women with disease causing genetic variants (with age to start and stop varying by specific mutation) or who are first degree relatives of such a variant carrier and those who have received chest or mantle radiation therapy between 10-30 years of age and completed treatment at least eight years earlier (NCCN, ACS, ACR, EUSOBI). [73]

Women with an estimated lifetime risk of ≥20% by risk calculators based largely on family history are also considered at high risk and it is recommended they have annual MRI screening in addition to mammography (NCCN, ACS, ACR, EUSOBI). [73]

With a lifetime risk exceeding ≥20%, MRI may also be appropriate in women with a history of lobular carcinoma in situ (LCIS) or atypical ductal hyperplasia (NCCN and ACR), those with a personal history of breast cancer aged 50 years and with non-dense breasts and for women with dense breasts (especially if extremely dense (EUSOBI) or with other risk factors.) [73]

A table highlighting the incremental cancer detection rate per 1000, the additional false positive rate and whether the modality of screening will detect interval cancers on the following page is evidence which causes us to want to make this submission, to want to model what the benefit would be of greater investment at the front of the pathway.

Outcomes from Supplemental Screening following 2D Mammography for Women with Dense breasts or (all Densities for MRI)

Method	Incremental Cancer Detection Rate per 1000	Additional False Positive Rate	Interval Cancers Reduced
US (first round)[a]	2–3 (73)	8%–12% (73, 81, 82)	Yes
US (subsequent rounds)[b]	1–3 (71,81,82)	2%–5% (71,81,82)	Yes
Contrast-enhanced mammography[c]	7–13 (66,67,83,84)	6.5% (66,67,83,84)	Unknown
MRI or abbreviated MRI (first round)	10–20 (55,57,64,82,85)	9% (55,57,64,82,85)	Yes
MRI (subsequent rounds)	6–7 (58,85)	2% (58,85)	Yes

[a]Performance characteristics of screening US are similar with handheld US, automated US, and semiautomated US.
[b]Includes results from screening US after tomosynthesis (71).
[c]Results reflect a mix of prevalence (first) and incidence (subsequent) screens.

Source: p.7. Implementing the National Dense Breast Reporting Standard, Expanding Supplemental Screening Using Current Guidelines, and the Proposed Find It Early Act [73]

The most common supplemental imaging tests and cancer detection rates are therefore mammography, handheld breast ultrasound (HHUS) and automated breast ultrasound (ABUS) with a non-significant increase if mammography is used alongside ultrasound, Digital Breast Tomosynthesis (DBT), Contrast Enhanced mammography (CEM), Abbreviated MRI (ABMRI) and Contrast Enhanced MRI(CEMRI). We are not aware of any Molecular Breast Imaging (MBI) in Aotearoa. Abbreviated MRI and CEM are screening technologies that can supplement mammography. These techniques have a specificity and sensitivity approaching that of MRI. Ultrasound may be used where cost limitations exist. More detail can be seen on, https://densebreast-info.org/screening-technologies/ and the following references [65,15].

We know some of these technologies risk call backs for additional screening, or vacuum assisted needle biopsies, which can lead to patient anxiety. **We believe that the concept of the "worried well" used in relation to breast screening does not in any way enhance women's health outcomes. Some of BCAC's members find it offensive, patronising, insulting and misogynist. It is absolutely unacceptable to withhold personal health information from women who may benefit from it because health providers don't want us to "worry".** This view is dangerous and becomes life-threatening and indeed fatal for some. The argument that low detection rates should mean no reporting at all could be applied to the BSA screening programme as a whole. Those with high density shown in mammograms have the greatest likelihood of having breast cancer and certainly have the right to have this information shared with them.

From our experience and our knowledge of the views of many New Zealand women, **women prefer to have been called back for a further test rather than have a missed cancer diagnosis.** This is supported by Stamatia Destounis, MD, FACR, FSBI, FAIUM, the managing partner of Elizabeth Wende Breast Care in Rochester, New York, Chair of the ACR Commission on Breast Imaging and a member of *Radiology Today*'s editorial advisory board.
https://www.radiologytoday.net/archive/rtMAY23p18.shtml

We acknowledge there are barriers to supplemental screening, such as the lack of precise guidelines, unclear reimbursement policies, limitations regarding referrals, resource and equipment to provide the screening, and potential additional expense and stress for the patient.

In reality, if we are going to inform women their mammogram is less effective because they have dense breasts, we need to inform them of the pros and cons of supplemental screening, which may include under and overdiagnosis alongside the risk of a cancer being masked.

The debate is ongoing regarding which women should receive supplemental screening and which modalities should be applied based on the level of their dense tissue and other risk factors. Globally many experts agree that women with dense breast tissue should have the opportunity to discuss their options with their healthcare providers. When New Zealand makes the decision to measure and report breast density, when all risk factors are considered, will more New Zealanders have access to the symptomatic pathway?

We suggest our biggest risk is not harm through overreporting but screening policy and guidelines that fail to recognise the risks of breast density and the need for supplemental screening. There is also a lack of recognition of this risk by insurance companies and a lack of understanding of the costs of failing to optimise screening at the front end of the pathway to avoid the high financial costs and human harms of late-stage diagnoses. Funding is at least needed for those who have a lifetime risk of 30% or over to be offered more intensive surveillance as a preventative strategy. This could potentially be provided through the Symptomatic Pathway.

A shared decision-making model is necessary, where the woman, healthcare provider and whānau work together to make the best decision on supplementary screening, taking into consideration the provider's knowledge and experience, evidence-based information about different options, and the patient's values and preferences.

The Royal Australian and New Zealand College of Radiologists (RANZCR) reporting guidelines for mammography do not enable a shared decision-making model. In fact, they deny New Zealand women this opportunity. "**This barrier to implementation of breast density measurement and reporting is of concern to BCAC".**

Prof. Christiane Kuhl says radiologists must be more active in providing objective and understandable information to women about the diagnostic and prognostic implications of dense breasts, and the value of using other screening methods. "Women must be enabled to make their own educated decisions and priorities. They have to be informed in an unbiased way about the individual need they have – and the diagnostic options they have – including the respective advantages and side effects of different screening methods," she told AuntMinnieEurope.com following the statement on 9 March by the U.S. Food and Drug Administration (FDA) to require reporting of breast density information by hospitals. "For instance, women must be informed about the recommendation to use MRI for screening when they have extremely dense breasts, even if insurance companies do not pay for it, or even if so far there is no national MRI screening implemented for women with dense breasts. Radiologists are experts in their field and must fill a leadership role, she continued. We should issue guidelines that are referred as such," [66].

Kuhl clearly supports BCAC's view that shared decision-making must be adopted in the field of screening, just as it has been adopted in the therapeutic arena. Her editorial, "What the Future Holds for the Screening, Diagnosis, and Treatment of Breast Cancer", was published in *Radiology* on 7 February 2023, as part of the U.S. journal's centenary celebrations.

Kuhl expressed her disappointment that the pressure to accept women as "grown-ups" had to come from an outside agency like the FDA. "My hope is that the current recommendations of the European Society of Breast Imaging (EUSOBI), suggesting that communication and shared decision making are important components of individualized or personalized screening, are used to change the field from within."

Ongoing education process

The updated FDA regulations are not really a surprise but rather a logical continuation of a process that has been going on for several years, Dr. Ritse Mann, chair of the EUSOBI scientific committee told AuntMinnieEurope.com. He thinks they will eventually help to improve education and information within Europe. Dr. Mann states "For screening organizations and policy makers, it simply becomes impossible to deny that breast density has an impact on the quality of breast screening," he said. "**Staying silent is likely to lead to legal actions against organizations unwilling to share density data with the women being screened**" [66].

FDA regulations do not generally have a direct impact on European practice, and they are likely only to be "a further argument in a discussion on honesty about and ownership of medical information that is slowly developing."

In essence, the U.S. authorities increasingly demand that women are informed of medical findings that may affect their risk of developing serious disease, Mann continued.

"To me, this is a logical continuation of the fact that women (and patients in general) are increasingly seen as owners of their own medical data," he said. "This process is also ongoing within Europe but is somewhat lagging behind" [66].

Research

New Zealand Research

In 2022 the Breast Cancer Foundation New Zealand (BCFNZ) published the 30,000 Voices publication [25], which highlighted ongoing differences in outcomes for our ethnic populations. As breast density is

not measured and reported we can only speculate on the role it may be playing in the poorer outcomes reported for Māori, Pacific, Asian and other high-risk women and younger women. The age at diagnosis also showed that too many women below the age of screening were being diagnosed Māori (17%), Pacific (21%) and Asian (23%). These were often late stage and high-grade leading to poorer outcomes.

If earlier diagnosis can be achieved across our population equitable outcomes will be more achievable.

Breast Cancer Cure, following consultation with Hei-Āhuru-Mōwai, has endeavoured to bring focus to the need to:

- Collect local data
- Focus on earlier detection and
- Investigate issues relating to access, age, breast density and personalisation.

The following projects have been under way since 2022:

One Size Does Not Fit All

This project involves Drs Annette Lasham and Nick Knowlton (who both analysed the data for the BCFNZ 30,000 Voices report [25]) and Prof Paula Lorgelly, health economist. They will provide a comprehensive analysis of breast cancer cases in Aotearoa New Zealand by screening and symptomatic diagnoses, including patient outcomes and the costs of each treatment pathway. They will make costed recommendations for any potential screening programme expansion, informed by equity considerations. This group have previously met with BSA and more recently met with Hei Āhru Mōwai and members of BSA's Pae Whakatere.

Personalised breast cancer screening in Aotearoa New Zealand

This is a small project designed to prepare for a larger research grant application planned for 2024 with a microsimulation focus. Drs Nokuthaba Sibanda, Annette Lasham and Nick Knowlton will carry out this 12-month research project between August 2023 and July 2024. It is focused on creating a research network, reviewing international evidence and a data investigation of potential benefits of personalised screening for particular risk groups. These researchers have also met members of Hei Āhru Mōwai and BSA's Pae Whakatere.

Risk stratification to assist modality selection.

Locally Dr Sugania Reddy, Specialist Radiologist at Mercy Radiology, has led a trial with Southern Cross investigating the use of IBIS (Tyrer Cuzik risk assessment), to stratify risk. The study aim was to determine the benefit of providing differing modalities to optimise screening strategy. This pilot will provide data that illuminates the benefit of supplementary screening for those at higher risk, including those with high breast density, for insurance purposes. Breast Cancer Cure is funding the publication of these results.

A study of Breast Density in the Symptomatic Pathway

A project previously led by Dr Monica Saini et al, will be reinitiated by Dr Ariane Chan. This BCFNZ funded project will provide valuable data regarding breast density on the Symptomatic Pathway, specifically Capital Coast Health.

Distance from Screening Facilities and issues of Access

The Lotteries Commission has funded a project led by Dr Annette Lasham focused on barriers to accessing optimal care including distance from facilities or the screening bus, choice of surgery and other barriers to accessing optimal care. The project will utilise GIS to better understand these issues across New Zealand.

AI/Breast Density

Funding has been sought for a project that aims to generate an invaluable breast density imaging dataset and a pipeline for personalised breast cancer screening, potentially leading to early detection and cost-effective treatment protocols. The study is both co-designed and co-led by Māori researchers.

Microsimulation

Planned for 2024 researchers propose a project that will develop a microsimulation model to test the opportunities and costs of moving towards more personalised and targeted screening.

Research into Breast Density is now a well-established scientific, epidemiological and technological discipline. It is important that we continue to monitor and learn from the wealth of information from outside New Zealand but it is also extremely important that we create the capacity, leadership and funding for local research if we are to tailor and operationalise policy to meet our unique needs.

Global Research

Volpara CancerX

A **New Zealand** company, Volpara Health (https://www.volparahealth.com/) was recently in 2023 as a founding member of **CancerX** (https://cancerx.health/about-cancerx/) a public-private partnership aimed at revolutionizing cancer innovation in the United States. **Cancer Moonshot** (https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative) and **CancerX** bring together diverse stakeholders with a singular focus on advancing innovative solutions for cancer prevention, treatment, and cure.

Reproductive factors

Jessica O'Driscoll, School of Public Health, **Ireland** looked at preliminary findings from the SPHeRE Study which is investigating the association between **reproductive factors and breast density** and found there was an inverse relationship between breast density and number of births, while the later the age of first birth the stronger the association with breast density. This is an issue often discussed although trial evidence has been scant [67].

Ancestry and breast density

Analysis of over 2.6 million mammogram results from the Breast Cancer Surveillance Consortium undertaken in the **US** population confirms greater prevalence of dense breasts in Asian women (66%) than non-Hispanic (NH) White women (45%), Hispanic women (45%), or Black women (37%). Breast density is inversely related to body mass index (BMI) and decreases with age and menopause.

After correcting for BMI, age, and menopausal status, Black women were more likely to have dense breasts than NH White or Hispanic women. https://www.ncbi.nlm.nih.gov/pubmed/37284771 [45]

Prevention and immune signalling

Kara Britt (Peter McCallum Cancer Centre, **Australia**) and Assoc. Prof. Wendy Ingman (Adelaide Hospital) acknowledge that biological studies **of mammographic density** open the door to new approaches to prevent cancer. Their study has demonstrated that immune signalling is a causal factor in high breast density and therefore associated with breast cancer risk. In the future they see the opportunity to tailor immunotherapy against immune cells for breast cancer prevention. Understanding the biological drivers will enable early intervention [67].

Increased risk of contralateral cancer from mammographic density

Gretchen Gierach, Deputy Chief of the Integrative Tumour Epidemiology Branch in the National Cancer Institute et al. researched the relationship between pre and post breast cancer diagnosis measures of mammographic density (MD) with contralateral breast cancer risk, within a community healthcare setting in the **USA**. This study focussed on understanding post treatment density risk. Two studies found a twofold risk. Elevated MD 1 year after diagnosis was associated with increased risk of contralateral breast cancer including higher stage (2-3) and grade (3-4). If MD dropped by 5% or greater the risk declined. This research continues [67].

Screening frequency and modality options for those with high breast density

Using over a decade's worth of data from BreastScreen **Norway**, researchers have found the highest rate of interval cancers among women with extremely dense breasts (4.33 per 1000 for VDG4 versus 0.4–3.0 per 1000 for VDG1-3). While women with extremely dense breasts (VDG4) constitute only about 6% of the screening population, they accounted for 14% of all interval cancers [70]. This supports the recent EUSOBI recommendations for more intensive screening regimens for this subgroup of women (Mann et al 2022 and references therein) [37]. See also https://www.eusobi.org/breast-imaging-publications-and-guidelines/

Women with extremely dense breasts also experienced shorter times from screening to diagnosis of interval cancer compared to women with other density categories (median 427 days for VDG4 versus 482–496 days for VDG1-3). Median time to interval cancer for women with extremely dense breasts was also closer to an annual screening interval compared to the more protracted median time to interval cancer for other density categories, supporting more intensive screening regimens for the former subgroup, suggesting annual mammographic screening would differentially benefit women with extremely dense breasts. While the recent EUSOBI recommendations suggest adding MRI every 2–4 years for this subgroup, annual mammography screening may be more feasible and possibly more cost-effective in low MRI-resource settings. **However,** among women with extremely dense breasts, over one-fourth (27.5%) of interval cancers were found among the prevalently screened women. **Thus, in low MRI capacity settings, an alternative strategy could be offering supplemental MRI or annual mammography screening for women found to have extremely dense breasts at their first or prevalent screening (versus women with extremely dense breasts undergoing subsequent screening).**

Future studies should focus on the use of AI on the subgroup of women with extremely dense breasts and investigate whether AI can effectively identify those women who should be offered supplemental MRI based on risk for interval cancer. The proposed alternative risk-based

stratification approach of offering annual mammography screening to women with extremely dense breasts may be beneficial in settings where MRI access is restricted [66].

SNPs, ethnicity and mammographic density

Only 39% of SNP's identified in European women are replicated in Asian women, Shivaani Mariapun, Cancer Research Initiatives Foundation, **Malaysia** [67]. **What are the implications for Māori and Pasifika?** A Genome Wide Association Study (GWAS) identified common variants associated with MD in Asian women, who have higher MD than European women. GWAS may uncover new loci. Larger studies are required on a wider range of ethnicities. The implications of different ancestry and SNP's is relevant for non-European New Zealanders should there be an opportunity to develop risk stratified screening models using SNP's. Research is needed on the New Zealand population.

Heritability of Mammographic Density phenotypes

Weiva Sieh, Department of Population Health Science and Policy and Department of Genetics and Genomic Sciences, Icahn School of Medicine, Mount Sinai, New York, **USA** described three Mammographic Density (MD) phenotypes: Dense Area (DA) in epithelial cells, stromal cells and collagen. Each DA increased risk of breast cancer. Non Dense Area (NDA) consisting of fatty tissue decreased risk of breast cancer independent of DA. Percent Density (PD) is the most studied measure of MD and increased breast cancer risk. All three DA phenotypes have genetic heterogeneity and show 60% heritability while the heritability of breast cancer is 27%. These distinct phenptypes are relevant to breast cancer risk and should not be ignored [67].

Healthy and risky dense tissue indicated by brightness on images is meaningful.

Andre Kahlil the University of Maine, **USA**, investigated the differences between healthy and risky dense tissue utilising spectrum technology, red being risky and yellow healthy. These are the brighter markings seen on MRI. This provides a visual indication that dense tissue is not uniform and reinforces the fact that we are not all the same [67].

Authors Declared interests: The author is Secretary, Breast Cancer Aotearoa Coalition; Chair, Breast Cancer Cure; Affiliate Breast Cancer Trials, Member National Breast Cancer QPI Working Group (2022-Present), Member BreastScreen Aotearoa Action Group (2023 ongoing), Member BreastSIG (2015-Present), Member Familial Breast and Ovarian Cancer Group (2022-Present).

The author was diagnosed with an interval cancer in 2013, four months following a mammogram resulting in the need for chemotherapy, targeted therapy and radiotherapy.

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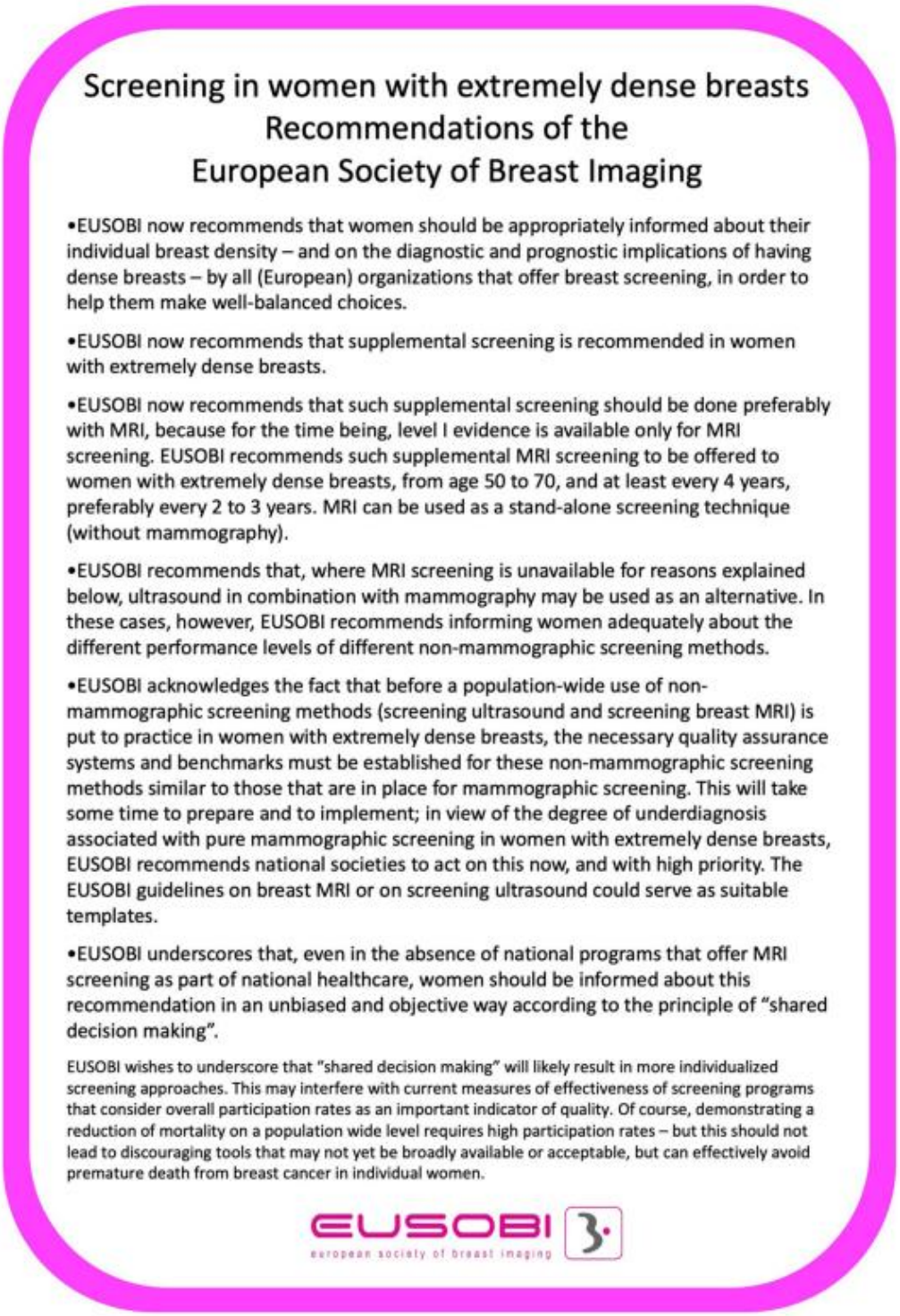
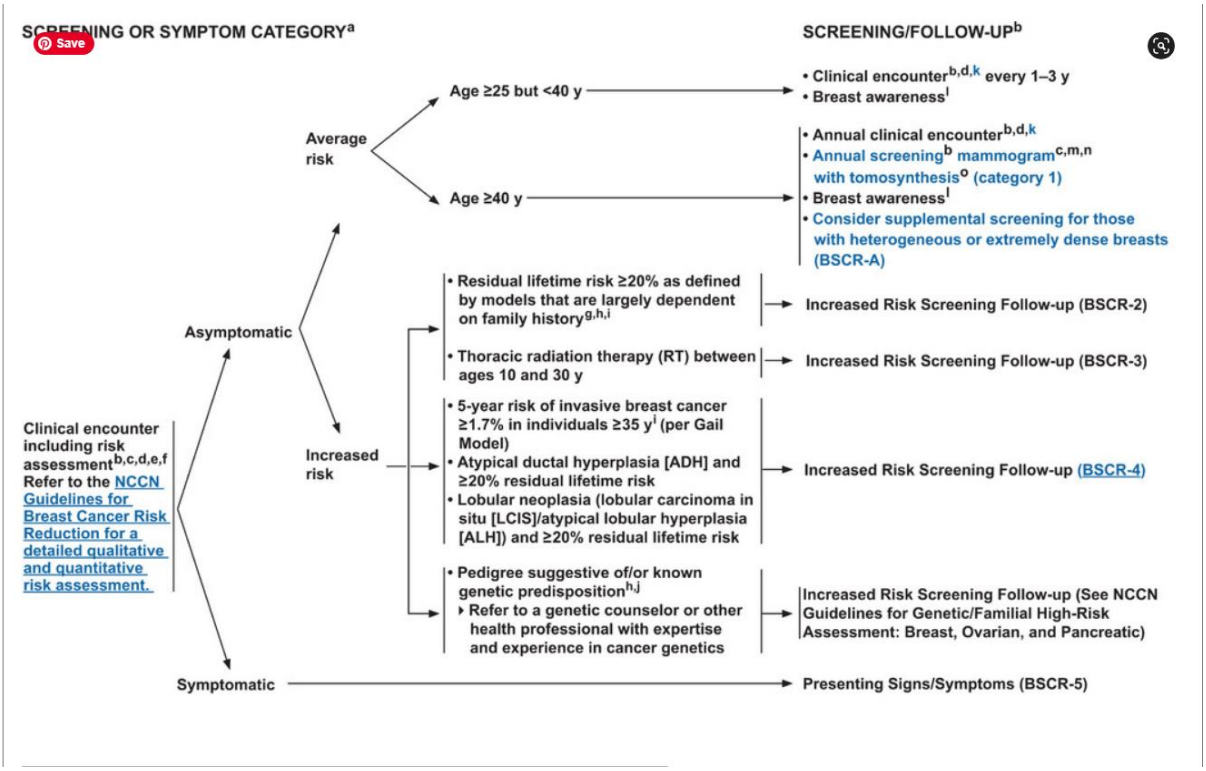
Appendix 1: Screening in women with extremely dense breasts: Recommendations of the European Society of Breast Imaging



Source: Mann, R.M., Alexandra Athanasiou, P.A. et al. 2022. Breast cancer screening in women with extremely dense breasts: Recommendations of the European Society of Breast Imaging. European Radiology 32, 4036-4045. https://link.springer.com/article/10.1007/s00330-022-08617-6

Appendix 2: National Comprehensive Cancer Network (NCCN) breast screening guidelines 2023



Source: NCCN Breast Screening and Follow up Guidelines, updated in 2023
https://www.nccn.org/professionals/physician_gls/pdf/breast-screening.pdf
(free membership and login required for access).