Moving Towards Personalised Breast Screening in New Zealand

A Pilot Study Proposal

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Moving Towards Personalised Breast Screening in New Zealand (Draft for Discussion)

The challenge

How we screen, when we screen, with what frequency and what is advised and reported needs a renewed focus and input from those leading, managing and participating in New Zealand's screening programmes. International evidence is now showing us the status quo is not serving us well enough.

The Society of Breast Imaging (SBI) in the US and American College of Radiology (ACR) Guidelines were recently updated (February 2020)[1] and they assigned a special status and approach for African American women and other women at higher than average risk for breast cancer. They now also call for all women to have a risk assessment at age 30 to determine whether screening earlier than age 40 is needed. SBI and ACR also newly-recommend that those previously diagnosed with breast cancer be screened with magnetic resonance imaging (MRI). Both groups continue to recommend that women at average breast cancer risk begin screening at age 40.

Debra Monticciolo, MD, FACR, Chair of the American College of Radiology Breast Imaging Commission stressed[2] "...scientific evidence now overwhelmingly supports a continued general recommendation of starting annual screening at age 40 alongside augmented and earlier screening for many women. The new guideline updates will help save more lives."

Let us review the factors that contributed to the ACR/SBI reclassification: African American women are at much higher risk for breast cancer. Monticciolo et al. (2018) report that these women are 42 percent more likely to die from breast cancer than non-Hispanic white women despite roughly equal incidence rates, have a two-fold higher risk of aggressive triple-negative breast tumours, are twice as likely to die of early breast cancers, and have a higher risk of BRCA1 and BRCA2 genetic mutations than those of Western European ancestry. [1]

Results from a New Zealand, University of Waikato study (Lawrenson et al. 2018)[3] showed serious inequities in breast cancer incidence and outcomes for Māori and Pasifika women.

- Pacific women diagnosed with breast cancer are twice as likely to die from the disease after 5 years than New Zealand European women. They are diagnosed with breast cancer younger than other groups, and the cancer is almost twice as likely to be an aggressive form.
- Māori women diagnosed with breast cancer also have a higher mortality (times 1.76) after 5 years than New Zealand European women. They are less likely to be diagnosed through mammographic screening.
- The greatest inequity occurs when women detect their cancer symptomatically i.e., they find it themselves rather than having it detected by screening.[14]

With these findings in mind we need to:

- enhance early diagnosis through more strategic, comprehensive tailored risk assessment programmes and report against those risks to improve outcomes

- incorporate different screening modalities ("supplemental or augmented"), at an earlier age for some, at greater frequency for those at higher risk and potentially less frequently for those at lower risk.

The challenge for New Zealanders is how can they know their level of risk when the current screening interval (two years) and age at which screening commences (45 years) assumes each woman has around the same cancer risk (average risk).[4.]

BreastScreen Aotearoa (BSA)[4] seeks to reduce New Zealanders' morbidity and mortality from breast cancer by identifying cancers at an early stage, to allow treatment to be commenced sooner than might otherwise have been possible. To determine whether we can adopt a more effective approach in New Zealand we suggest a pilot study that could lead to a trial.

Internationally there are four relatively new trials taking place which focus on personalised screening. These trials are a response to four earlier trials which together created a body of evidence and new information highlighting possible improvements to be made to screening programmes globally [21, 22, 23, 24].

- Personalised Mammography Screening to Improve Detection of Breast Cancer (Professor Ian Campbell, Victoria, Australia) [5]
- Wisdom Study, Dr Laura Esserman, University of California and Stanford Health North West (US)[6]
- My Personalized Breast Screening, Suzette Delaloge, MD, France (MyPeBS) (Europe +Israel) [7]
- CanRisk (UK), Antoni Antonio, University of Cambridge [8]

What do these trials have in common? They all seek to improve outcomes by complementing or optimising population-based screening programmes. They utilise differing risk-based tools to identify who may have higher than average risk at an earlier age, have heterogeneous or extremely dense breasts, family history or genetic, clinical and lifestyle differences. They are seeking to improve outcomes by identifying whether, with a different focus for those with higher-than-average risk and new ways of interacting with consumers (incorporating on line, via primary care or via screening units), better outcomes could be achieved. Is it possible to achieve better outcomes than are currently the case with a national screening programme comprising a mammogram every two years from age 45 to 69 for all New Zealand women?

Epidemiological studies in New Zealand suggest the current system may result in breast cancers being found too late, at an advanced stage, in women who potentially may have been predicted to be at higher than average risk. They and global studies and trials also suggest others at lower-than-average risk may not need to be screened as intensely as those at high risk. Some of the trials also seek to improve equity by tailoring screening to risk.

Issues these studies seek to resolve include:

- *Do all women have the same risk of breast cancer and what differences, for example breast density or ethnicity, may require a focus?*
- *Can women be separated into low, medium, and high-risk groups?*

- *Is it useful for those conducting screening to interface with women directly; can women themselves either alone or with their GP or a remote counsellor assist in identifying their risk?*
- *Given good information with the option of support, can women modify some of those risks?*
- *What is the age at which screening should begin and cease for groups with different risk profiles?*
- *What is the frequency with which women with different risk profiles should be screened?*
- *What modality or method of screening should be used under differing risk scenarios?*
- *Can high and low risk abnormalities and probabilities of metastasis be identified?*
- *How can technology be used to achieve optimal screening?*

What is the case for change in New Zealand and what are the issues?

The current population-based screening programme was established to provide a service to women at average risk of breast cancer. In New Zealand we screen women between the ages of 45 and 69 every two years[4], with an intention to extend to 74 years (an intention which has been in place for some time but has not yet been realised).

New Zealand's breast screening policies are similar to Australia's breast screening programme (aside from Western Australia where breast density is measured and reported). Australia is currently reviewing its position statement on breast density; it is yet to make its findings known.

1. *Inequity is evident in New Zealand's screening statistics[9].*
    - New Zealand's breast screen statistics cover only those aged 50-69 and specifically exclude 45-49-year olds for whom there is no report.
    - BSA's December 2018-December 2019 report suggests ongoing screening coverage issues for Māori in Auckland (58.9%), Waikato (58.4%), and Taranaki (63%). The target is 70%.
    - Better coverage for Māori is being achieved in Nelson Marlborough (74.9%) and Whanganui (74.1%).
    - For Pacific women, Counties Manukau (82.7%) and Bay of Plenty (74.5%) are performing very well while other regions less so.
    - For Asian women, no region is performing well, with South Canterbury and Southern performing the worst at 30.8% and 35.1 % respectively.
    - For all ethnicities combined, Waitematā, Auckland and Waikato were not achieving 70% while all other regions were, with Whanganui the top performer.
    - Rescreening targets of 70% are not being met: 55.7% of Māori and 56.1% of Pacific women received rescreening and 68.1% of other ethnicities. Poor rescreening statistics may result in late detection of cancer, leading to worse outcomes.

2. *New Zealand's statistics exclude younger women. This is likely to increase inequity for Māori and Pacific women and those at higher risk.*

With BSA not reporting on women aged 45-49 years we lose highly relevant data. By screening for the 'average woman' in the 45 – 69-year band, we exclude those who develop their cancer at a

younger or older age. The younger group is at particular risk. Statistics from the February 2020 Annual Report of Sweet Louise (a charity supporting women with advanced breast cancer) [10], show that 22% of its members are under the age of 49.

Evidence of earlier onset of breast cancer for Pacific women and later diagnosis for Māori women suggests New Zealand's breast cancer screening is not optimised for these groups (Seneviratne, 2016)[11].

The New Zealand Breast Cancer Registers are instructive for understanding inequities in breast cancer outcomes for Māori (Lawrenson et al. 2018) [3] (Tin Tin, Elwood et al. 2018)[12] and Pacific women (Brown, Lao et al. 2017) [13].

3. *New Zealand statistics do not report symptomatic cancers identified through a screening failure as distinct from a failure of participation.*

At the Waikato Breast Cancer Research Workshop, November 2019, Prof. Ross Lawrenson highlighted that the greatest inequity occurs when women detect their cancer symptomatically i.e., they find it themselves[14]. The detailed analysis also indicates that we may be finding too many of the more worrying cancers too late indicating we are either not screening early enough for some women or with the correct modality/frequency for others, or there may be an issue with participation in our breast screening programmes.

4. *New Zealand's breast screening policy settings for advising and reporting breast density and other risks raise ethical questions.*

Breast density affects a woman's breast cancer risk and the sensitivity of a screening mammogram. It can only be reported by a radiologist. Women cannot determine it from the look and feel of their breasts. BSA (NZ), BreastScreen Australia and the Royal Australian and New Zealand College of Radiologists do not require women to be advised of their breast density.[15] New Zealand's breast screening programme is highly reliant on digital mammography and is not augmented with supplemental screening based on risk. In addition, BSA does not advise women of their density, nor collect or hold data regarding breast density or other risk factors. We understand this is partly driven by system and/or resource limitations.

What are the ethical issues associated with breast density notification as they relate to equitable care, patient knowledge in decision-making, duty of care by a physician? BCAC seeks a policy framework which takes better account of these issues, given the evidence now available.

For example, a 2013 study involving 3,000 women showed that Māori women may have greater volumetrically dense tissue in their breasts than Pasifika, Pākehā and Asian women.[16]

The Lifepool project (54,000 women within this database) in Victoria Australia led by Prof. Ian Campbell has demonstrated many people have little understanding of their own risk and this project seeks to better understand those risks.[17]

In the absence of new or improved systems, online enrolment in trials utilising risk assessment methods would be one way to elicit new information for the New Zealand population and may also resolve resource issues.

5. *New Zealand's National Screening Unit (NSU) places a heavy emphasis on not wanting to "initiate changes which may increase false positives or overdiagnosis and cause anxiety or stress to women" alongside a concern for "do no harm" (Dr Jane O'Hallahan's presentation at Cancer Care at a Crossroads 2019).[18] The NSU continues to turn away from recently published evidence regarding breast density, and newer forms of screening such as abbreviated MRI, contrast mammograms and new risk assessment tools as a means of identifying those who are at higher than average risk, and to begin to resolve ongoing inequities through earlier diagnosis.*

Given a growing body of evidence regarding screening sensitivity and specificity of different screening modalities for differing levels of risk, consideration of the personal and economic impact of treatment when a cancer is not detected early needs consideration alongside the current focus on participation levels and concerns about false positives and potential over-diagnosis. There is no need to treat a false positive and as shown below false positives diminish significantly in the second year and subsequent years for most modalities as demonstrated in the DENSE trial (Bakker et al, 2019)[19]. A critical question in assessing the effectiveness of the current BSA screening system is whether it is successfully identifying the most aggressive cancers on a timely basis to achieve early diagnosis and reduce mortality. For example, BSA in its density information sheet highlights that the risk of the masking effect of breast density is "less since the programme has become fully digital."[20] This is concerning given the evidence presented below. BCAC advocates that BSA should measure and record breast density and be required to inform women of this and any other known relevant risk factors. The collection, reporting and collation of this data would enable earlier detection, reduction in avoidable interventions and improvement in mortality statistics for New Zealand women.

Taking the above into account we in New Zealand urgently need to develop a study that will generate new knowledge on these issues for our population.

In doing so it is important to recognise information available from four significant trials which have reported in the last two years (PROCAS 1 and 2[21]; MRISC**[22]**, FaMRisc[23] and DENSE**[24]**) and other evidence available globally which have all informed the development of the four trials already mentioned, Personalised Mammography Screening,[5] WISDOM[6], MyPeBS [7], and CanRisk [8].

The evidence

- Mortality reduction has been proven for mammography and increasingly Digital Breast Tomosynthesis (DBT) over Digital Mammography (DM).[25] The key issue is the imperfect sensitivity of digital mammography (DM) which reduces the effectiveness of screening. DBT is more likely to be a cost-effective alternative to mammography in women with dense breasts. Whether DBT can be cost-effective in a general population depends on DBT costs but it needs to have a sensitivity of 90% for cost effectiveness to be sustainable. [25]
- The ASTOUND-2 prospective trial compared cancer detection rates in women with dense breasts who have received a negative result from DM, when adjunct screening was performed using either ultrasound or DBT. This showed an incremental cancer detection rate of 2.83 per 1000 screens for DBT compared with 4.9/1000 for ultrasound. Additional false-positive recall was 0.30% for tomosynthesis vs 1.0% for ultrasound. [26]

- Screening with MRI improves survival for women with familial risk of breast cancer (age 35 to 50 years) by 25% at US$134,932 (€102,164) per life year gained (LYG) compared with 17% mortality reduction at US$54,665 (€41,390) per LYG with mammography only (MRISC Trial).[22]
- MRI detects significantly more cancers and at a relevant earlier stage, than mammography alone. Furthermore, MRI-screened patients had fewer large and node positive cancers and fewer interval cancers (cancers occurring between screening events) (FaMRisC).[23]
- Supplemental breast MRI screening to measure breast density resulted in an improved cancer detection rate of 16.5/1000 with a significantly reduced interval cancer rate of 0.85 compared to digital mammogram alone with detection of 5.06/1000 (DENSE, 2019[24]).
- MRI performs better and detects biologically significant cancers earlier than mammography for those at higher risk, excluding some patients with BRCA2 mutations (Jochelson, SABCS, 2018)[27].
- Breast cancer risk-stratified screening is seen as ready for implementation if breast density and single nucleotide polymorphisms (SNPs) are included in the risk assessment (BODICEA. 2019)[28] (The PROCAS team, SABCS, December 2018).
- Annual screening detects breast cancers earlier than less frequent screening for women at medium to high risk of breast cancer. Those with a family history and aged 35 to 39 had significantly smaller cancers detected and were less likely to have had their cancers spread to the lymph nodes (PROCAS). [21]
- Use of abbreviated MRI[27, 29] (14 min. vs 42 min.) demonstrates adequate sensitivity and specificity (85% and 89%) in the differentiation of benign and malignant breast lesions. When combined with Dynamic Contrast, the MRI false positivity rate is decreased. The basic European breast MRI takes 42 minutes; an abbreviated protocol would take 14 minutes and an unenhanced protocol six minutes. 2D and 3D (whole slab) protocols performed similarly to each other with just a 0.1% difference in detection rate. The results demonstrated benefit across all levels of the breast density scale (A, B, C, D) with critical improvements in C and D, the groups with the highest density.
- On a mammogram, breast density (also known as mammographic density) is shown as white and bright regions. The American College of Radiology describes four categories of density in the BI-RADS Atlas (5th Edition) ranging from 'Mostly fatty' to 'Extremely dense'. Almost 8% of women aged between 40 and 74 years have 'Extremely dense' breasts, and 35% have 'Heterogeneously dense' breasts. The sensitivity of mammography to detect breast cancer is reduced in women with dense breasts, as potential tumours, which are shown as white on a mammogram, can be masked by the white dense regions. It is also known that breast cancer is more likely to develop in women with dense breast tissue. Women with breasts classified as 'Extremely dense' are 4–6 times more likely to develop breast cancer compared to women of the same age and body mass index whose breasts are classified as 'Mostly fatty'.[30] As reported in www.DenseBreast-Info.org, the law in the USA directs the FDA, through a regulatory process, to ensure that mammography reports received by patients and their screening providers include appropriate information about breast density. A recent study also identified that automated and radiologist-assessed BI-RADS density similarly predict interval and screen-detected cancer risk, suggesting that either measure may be used to inform women of their breast density (Kerlikowske, K et al, Annals of Internal, 2018).[31]
- In other findings Dr Maxine Jochelson, from Memorial Sloan Kettering Cancer Centre, reports that BRCA1 differs from BRCA2 in that mammography is less sensitive in detecting BRCA1 at 25%

vs 61.5% (SABCS, 2019)[27]. BRCA1 has more benign mammographic appearance, a lower proportion of Ductal Carcinoma in Situ (DCIS) and a higher proportion of interval cancers, particularly triple negative and cancers with larger tumour size at diagnosis. BRCA2, although MRI sensitive, also is sometimes only found by mammogram as BRCA2 is histologically more like sporadic cancers in its appearance (Rijnsburger et al, 2010 JCO[32]).

Are we all at the same risk?

Our current approach in New Zealand assumes that all women have the same average risk of breast cancer. Several years of trials have clarified that breast cancers vary in terms of timing of onset, ease of detection, rate of growth, probability of metastasis and that everyone differs biologically, genetically and through their lifestyles.

By investigating tailored screening based on a person's specific risk (high, medium, or low) rather than average risk, new data could be generated to inform best practices.

ACR (Monticciolo, 2018)[1] recommends that for those with:

- Genetics based increased risk (and their untested first-degree relatives) or a calculated risk of 20% or more, DM with or without DBT should be performed annually beginning at age 30.
- Histories of chest radiation therapy prior to age 30, DM with or without DBT should be performed annually, beginning at age 25 or 8 years after radiation, whichever is later.
- Genetics based increased risk (and their untested relatives), histories of chest radiation (≥ 10Gy) before age 30, or a calculated risk of 20% or more, breast MRI should be performed annually beginning at age 25-30.
- A history of breast cancer and dense breast tissue, or those diagnosed before age 50**,** annual surveillance with breast MRI is recommended.
- A history not included above or with atypical ductal hyperplasia, atypical lobular hyperplasia, or lobular carcinoma insitu, MRI should be considered especially if other risk factors are present.
- All others, especially black women, and those of Ashkenazi Jewish descent, should be evaluated for breast cancer risk no later than age 30, so that those at higher risk can be identified and can benefit from supplemental screening.

ACR no longer intends to treat everyone the same. They recognise that, for their region, the above changes will improve early diagnosis and lower mortality for those of above average risk in their population.

What change is needed in New Zealand?

Risk stratification models

The models used to assess risk vary from Gail[33] to IBIS[7] and BODICEA[28] as examples. These objective tools identify differing levels of risk to enable the earliest possible detection of breast cancer and

therefore best outcomes from monitoring and its treatment. Factors include for example within BODICEA[28]:

- The effects of truncating variants in BRCA1, and BRCA2 (high penetrance variants) and PALB2, CHEK2, and ATM (rare, intermediate risk variants).
- A Polygenic Risk Score based on 313 single-nucleotide polymorphisms (SNPs) explaining 20% of breast cancer polygenic variance (conferring lower risks but with substantial levels of stratification in the population)*;* breast cancer risks associated with SNPs can be conveniently represented as a polygenic risk score (PRS). However, the known genetic factors explain only about 45% of the observed familial aggregation.
- Known lifestyle/hormonal/reproductive risk factors, (e.g. age at menarche, age at menopause, parity, and age at first live birth), exogenous hormonal factors (e.g. use of oral contraceptive and use of postmenopausal hormone replacement therapy (HRT), anthropometric factors (e.g. height and body mass index), and lifestyle factors (e.g. alcohol intake) (collectively referred to as risk factors are questionnaire-based risk factors). Each of these risk factors has only a modest effect on cancer risk, but in combination and with family history and known genetic factors, they can improve risk stratification. Moreover, as some of these factors can be modified, and used in the counseling processes to guide at-risk women on possible risk-reducing options through changes in behaviour or lifestyle (e.g. reduction in BMI, alcohol intake, or HRT use).
- Mammographic density and other relevant information.

The greatest breast cancer risk stratification is achieved when all genetic and lifestyle, hormonal, reproductive, anthropometric factors are considered jointly. With all factors, the predicted lifetime risks for women in the UK population vary from 2.8% for the 1st percentile to 30.6% for the 99th percentile. 14.7% of women are predicted to have a lifetime risk of ≥17 to 30% (moderate risk [NICE] guidelines) and 1.1% to have a lifetime risk of ≥30% (high risk).

There has been no examination of the proportion of New Zealand women who fall into the moderate to high risk groups although Walker et al., (2017) [34] proposed that successful genetic screening in New Zealand would require tests with increased sensitivity and specificity. They identified a subset of BRCA1 mutation carriers which shows a higher expression of BRCA1 mRNA compared to non-carriers. This finding has led to a new method of identifying high risk breast cancer patients. Analyses are ongoing for BRCA2 and in 2019 the team broadened their study to include BARD1, CDH1, CHEK2, PTEN, PALB2 and TP3, using nanopore sequencing. It is expected that outcomes when published will be integrated into international guidelines. In the future this work could be extended to moderate and high-risk genes to better understand potential differences across Māori and Pacific populations, for whom there are currently no reliable norms and to better understand our entire New Zealand population.

If New Zealand is to make significant improvements in our population-based breast screening, we need to recognise, measure and record a broader range of risk factors, seek to better understand the nature of risk in New Zealand women of different ethnicities and progressively tailor our screening programme to deliver an appropriate level of surveillance to women in all risk categories.

How often should we screen and at what age?

Dr Maxine Jochelson indicates screening every six months from age 25-30 for those with BRCA1 mutations but the recommendation for those with BRCA2 is less strong.[27] Alternating MRI and screening at six-month intervals beginning at age 30 years was identified as clinically effective and more cost-effective in BRCA1 gene mutation carriers compared with BRCA2 gene mutation carriers.[35] More recently from a 2018 prospective study of high-risk patients of whom 65% were BRCA1 mutation carriers given six-monthly MRI/annual mammogram, the recall rate was less than 7% with 13 invasive cancers and four DCIS identified. Eight of13 Invasive Ductal Carcinoma were seen only on MRI and five on interval rounds. There were not enough cancers in the BRCA2 group to recommend 6-monthly MRI (Guindalini et al, CCR 2018). [36]

For BRCA1 and other high-risk mutations the most effective screening paradigm is likely to be MRI twice a year from age 25-80, while some breast cancer survivors can stop screening at an earlier age. (Jochelson, 2018)[27].

She adds that previously irradiated patients, for example those with Hodgkin's Lymphoma, should receive an annual mammogram and MRI alternating every six months to ensure early detection as, for them, treatment options are more challenging and it is important that the cancer is detected early.[37]

A pooled analysis from six studies showed for mutation carriers MRI brought equal benefit to those over 50 and younger women. Phi et al, J Clin Oncology 2015.[38]

Some questions for New Zealand that could be answered by research include:

- Would better understanding our populations' risk of breast cancer better inform our policy settings for screening (including those previously diagnosed with breast cancer) and lead to a more tailored approach to screening based on risk?
- Would such an approach assist New Zealand women to understand their risk of breast cancer at a younger age and enable them to initiate and participate in an appropriate level of screening and monitoring based on that risk?
- If women chose to be advised of their breast density and other risk factors would this facilitate augmented screening for those who need it and reduce interval cancers and late diagnosis as local epidemiological studies tell us?
- Would this assist Māori and Pacific women and others with higher than average risk whose cancer is being detected too late and at an advanced stage?
- Would keeping and reporting statistics beyond participation better enable us to understand whether optimised screening in New Zealand with timely initiation, frequency and the correct modality based on risk would result in early diagnosis and reduce mortality?
- Would new and improved technologies make optimised screening cost effective, provide better support and assist with the ease of implementation relative to late diagnosis and ongoing treatment for both Māori and Pacific women and those at above average risk?

What modality or method should we use?

MRI is seen as the most sensitive test available. It finds approximately 97% of all cancers that are present, i.e. it only misses 3%. MRI sensitivity is not limited by breast density and delivers no ionising radiation. It works by enhancing contrast dye movement. Specificity is 63%, i.e. it can identify those with breast cancer in 63% of cases but can give a false positive in 37%, requiring further investigation. MRI preferentially detects higher grade lesions and results in a reduced interval cancer rate when compared with mammography[27]. In NZ it costs approximately $2,000 (EU600 and US$4,000)[27]. There is some concern regarding gadolinium brain deposits. There is also concern about false positives, but these are seen to reduce significantly in subsequent years. The differing regional costs have driven innovations, with the US now progressing Abbreviated MRI and Contrast Enhanced Mammogram as alternatives to MRI. These may also be very relevant for New Zealand due to their cost effectiveness and clinical efficacy.

Abbreviated breast MRI is seen as a positive alternative, comprising: a decrease in magnetic resonance and technologist time to less than 10 minutes; with a decrease in reading time and cost it is estimated to cost US$300-500 (NZ cost not yet attainable), at the same time accompanied by an increase in detection rates; and an increase in detection of higher grade lesions. Kuhl et al, J Clin Oncology, 2014[39] showed sensitivity of 100% and specificity of 94.3 %. Van Zelst et al, Investigative Radiology, 2018[40] demonstrated abbreviated breast MRI compared well with full MRI.

CEDM (Contrast Enhanced Digital Mammography) is also seen as an excellent alternative by Dr Jochelson[27] and is performed after an injection of iodine as a contrast dye. Low and high energy mammograms are performed almost simultaneously. The image can be filtered so that the breast tissue is no longer visible, but other structures such as the vascular system can be seen, and this reveals some lesions which cannot be seen in the unfiltered image. A low energy image is equivalent to a normal mammogram and the iodine image is nearly equivalent to MRI in its ability to detect lesions (Covington et al, ajronline.org.,2018)[41].

Digital Breast Tomosynthesis (DBT) has largely replaced mammography in the US although not to the same degree in New Zealand where digital mammography is the standard in BSA's screening programme. With DBT 1.5 to 2x more cancers are detected than with digital mammography.[1]

Whole Breast Ultrasound has been shown in multiple studies to improve cancer detection in women at elevated risk. ACRIN 6666[42], a large prospective multicentre study evaluating women at elevated risk (most having dense breasts in combination with other risk factors), found a supplemental cancer detection rate of 4.3 per 1,000. The cancers found by ultrasound tended to be invasive, small (median size, 10 mm), and node negative (96%). However, this was accompanied by an increase in false positive findings and lower positive predictive value (PPV) for biopsy compared with mammography or MRI. Recent studies suggest as the technology matures, some of its drawbacks may diminish. Weigert, as reported by Monticciolo [1] noted that PPV increased from 7.3% in year 1 to 20.1% by year 4, with a stable cancer detection rate often reliant on high physician expertise and experience as well as availability of prior examinations for comparison. Advances in automated breast ultrasound may address constraints of operator dependence and labour intensity.

Molecular Breast Imaging (MBI). The Mayo Clinic is using MBI, a technique that uses the LumaGEM, FDA-cleared Molecular Breast System utilizing cadmium zinc telluride (CZT) technology for breast imaging. MBI has been found to be three times more sensitive at identifying breast cancers when compared to mammography. MBI has matched MRI, with 91% and 69% sensitivity for tumours 5mm or less (dual head) and 90% sensitivity to tissue abnormalities with diameters of 5 to 20 mm. MBI "exposes cancers that may not be identifiable with mammography or ultrasound; both modalities have their differences, some good and others bad," says Michael K. O'Connor, PhD, of the department of Internal Medicine at Mayo Clinic. O'Connor notes that while MBI requires radiation, it is five times less expensive than MRI and is a "far simpler technology to both install, use and maintain." The majority of MBI research is currently directed at using it as a screening tool for dense-breasted women. Outside of screening, MBI is being looked at as a means of monitoring breast cancer therapy, looking at MBI when performed before and after neoadjuvant chemotherapy administered before mastectomy. "Results are promising. Ongoing trials are required but it appears to be developing a role as a supplemental tool alongside mammography for women who have dense breast tissue," says Deborah J. Rhodes, MD, of the Internal Medicine and Division of Preventive and Occupational Medicine at Mayo.[43]

We often hear the suggestion that women will worry unnecessarily if they are offered supplemental screening. Preliminary results from Western Australia, where density has been reported to women for 10 years, and a survey by Stone et al, 2018[44] showed that learning about their risk did not increase anxiety in around 60% of women with dense breasts. Anxiety did not appear to deter women from attending screening, with more than 96% of women who felt anxious indicating they intend to be screened, when next due. Preliminary results also showed that around 17% of women notified have had a supplemental ultrasound due to their breast density, 2/3 of women interviewed were glad to be informed and more likely to be compliant with recommendations. BCAC believes that women have a right to know their breast density and associated risk.

The Australian Government Department of Health has in April 2020 funded Cancer Council Australia to explore options for risk-based, personalised approaches to breast cancer screening in Australia. Having completed environmental scans in 2019, they intend to update evidence, complete systematic reviews including density, review and evaluate trials, evaluate clinical and health economic modelling and review BreastScreen's jurisdiction and value of practices, with the intention to optimise the early detection of breast cancer [45]. Will there be benefits in trans-Tasman studies or trials? Is equity of concern in Australia?

Early detection of breast cancer can be achieved through breast cancer screening programmes but over the last 20 years it has become increasingly clear that women have varying degrees of risk of developing breast cancer and our screening programmes would be more effective if they were tailored to individual risk. The ACR and SBI new guidelines indicate that the evidence is now in to support such initiatives.

In conclusion

The ACR and SBI screening guidelines have recently been adapted to incorporate improved strategies for risk-stratified breast cancer screening. These changes have responded to growing

evidence of benefits of a smarter approach, along with ongoing challenges from researchers and consumers globally. There is an ongoing need for research to ascertain the best approaches to adapt existing and emerging risk prediction tools for breast cancer and its biologically heterogeneous subtypes.

We in New Zealand should retrospectively and prospectively study options for new targeted breast cancer screening programmes. Trials mentioned above demonstrate the urgent need to better understand our population now rather than relying on data from other countries. In particular, our Māori and Pacific populations will not be well served by such reliance and nor will those at higher than average risk.

Dr Jochelson asserted at SABCS that data now shows that we need to tailor our screening to the level of risk through cost effective tools. She reiterated that the status quo is not acceptable. The recent SBI and ACR guidelines are significantly more tailored for those at above average risk and provide examples of improvements that could be made to the BSA screening programme in New Zealand.

BCAC acknowledges that improving breast cancer outcomes involves a wide spectrum of activities and in this instance, we focus on screening in order to identify and reduce inequities as people enter the screening and diagnostic pathway within the public health system. Other considerations include the cost-effectiveness of different approaches, recognition of the limitation of mammographic screening for those at higher risk and the benefits and challenges posed by the implementation of innovative approaches.

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