PRECISION HEALTH NOW AND IN THE FUTURE

Author Fay Sowerby

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BREAST CANCER AOTEAROA COALITION SUBMISSION

5 Fitzroy St, Ponsonby, Auckland 1021

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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. We agree that precision health, including precision medicine and integral components including tools and technologies, require urgent focus to enable innovation in the near and longer term. Bringing focus to the various elements of precision health will lead to development and improvements across our health system, through ongoing research and clinical trials.

We see New Zealand's purposeful adoption of precision health, including precision medicine, as vital to improving New Zealanders' health outcomes and we welcome this opportunity to contribute to this consultation as Aotearoa progresses from the status quo.

It will be helpful to better understand elements that impede or may impede progress by enabling broad input and discussion, so that as the adoption of precision health progresses, we develop and grow our shared understanding of the value its interdependent components will add to the health system and our lives.

This is important for all health conditions. As a breast cancer charity, we are aware that cancer is the greatest cause of health loss in Aotearoa New Zealand with approximately 25,000 people diagnosed every year. Cancer is also the leading cause of death, with 9,000 people dying each year.

Prevention comes in two forms: *reducing the incidence of cancer* and *reducing late diagnosis* to ensure that the cancer is less likely to recur. Both forms of prevention are critical to precision health however different cancers present different opportunities for prevention whether they be behavioural or biomedical in nature.

Precision medicine utilising new technologies is essential to achieve best possible outcomes in longevity and quality of life, and this is an integral element of precision health. All elements are required for precision health to be transformative.

There is an opportunity to bring about transformative change through risk stratification, prevention, early detection, improved diagnosis, prognostics and treatment. Greater precision across all aspects of the pathway will improve both quality of life and survival.

It is therefore important that disease risk reduction efforts be **coupled** with comprehensive control strategies that include efforts to support early diagnosis and effective treatment with policies and guidelines tailored appropriately to local cancer risk factor burden.[1]

In New Zealand in breast cancer and many other diseases we see too many Māori, Pacific and Asians diagnosed late stage[2]. For diseases diagnosed as early-stage, treatment is more effective and affordable, better tolerated, and practical to administer in restricted-resource environments.

In breast cancer, we are on the cusp of seeing a growing range of tools from cfDNA[3] to predict risk, to risk stratification through BOADICEA (CanRisk) [4] and IBIS (Tyrer Cuzik) [4] (which include family history, lifestyle/hormonal risk factors, common genetic susceptibility variants, and mammographic density combined), to identify who needs greater surveillance to ctc, ctDNA to diagnose, prognose and monitor risk of recurrence for early intervention and treatment. [6,7]

Such models will better inform patient, whānau, clinician and community decisions regarding who is at greatest risk and who will need surveillance and tailored and more nuanced approaches than those at low risk who may need less follow up.

Increasingly we also see indications that ctc and ctDNA will be used in early high-risk breast cancers to detect residual disease and to detect and treat early resistant mutations e.g., ESR1 (wild type and endocrine driven), AKT, PIK3CA/mTOR or PARP as ESCAT approvals increase. [6,7]

In addition, precision will reduce the number of patients being treated with surgery, medicines and radiotherapy who will not benefit from these interventions.

The opportunity we see, is New Zealand confidently moving from a dedicated Population Health approach to one which increasingly incorporates Precision Health including Precision Medicine. This will be made possible by addressing barriers enabling progress at a legislative, policy, leadership, cultural/ diversity, operational, technology and infrastructure level including funding to build capacity and capability.

A future vision for Aotearoa

In a future Aotearoa where Precision Health has been embraced and enabled, there will be funded access to new and existing technologies validated on our population through increased participation in research and clinical trials. Health economic analysis will reveal benefits available to whānau and the health system as a whole, of a targeted approach through risk stratification, focussing more on those at above average risk who will benefit from earlier intervention (Māori, Pacific, in some cases Asian and others at higher risk) , providing more precise monitoring and surveillance and utilising new technologies and computational methods to achieve a curative approach to some diseases.

Funding will have been sourced to develop the necessary infrastructure and to build capability and capacity to support these changes. Earlier and more refined diagnoses will then be possible.

There will be options for managing rare diseases and hereditary conditions.

Inequities will be reduced and Aotearoa will be contributing globally to a better understanding of ancestry-specific health measures for Māori, Pacific and Asian people in the Pacific.

New Zealanders will be better informed and educated about their health and will be key stakeholders in this new approach.

The barriers to be overcome to enable a move to Precision Health including Precision Medicine include policy leadership to facilitate an approach to prevent genomic discrimination and to better enable gene editing. New Zealand sits separately from other OECD countries in this regard.

We will have funded, supported and enabled a national 10K genome project built on the genomic medicine pathfinder Rakeiora, enabling us to research and trial innovative new options for our population. Governance, Te Tiriti and data sovereignty issues have been resolved so that genomic testing at birth and wellness genomic tests at age 30 are seen as offering benefit to New Zealanders at higher risk. While participation will not be compulsory, those involved will have access to the necessary guidance and support. We will have mainstreamed genetic counselling.

Through research and clinical trials, new tools, technologies and approaches will be validated for our population across the cancer and other disease pathways for prediction, risk stratification, early

detection, and prognostics along with monitoring and surveillance. We will intervene early and treat precisely.

We will have eliminated barriers for those at both high and moderate risk of hereditary or rare conditions, recognising that new technologies will be available to assist those impacted by these conditions to both prevent and avoid late diagnosis, along with demanding treatment regimens required with late diagnosis.

We will partner and collaborate with the best and as a result we will diagnose and treat early. Computational biology capability and capacity will have been grown through collaboration between scientists and clinicians to combine expertise.

Computational Pathology will have an ethical framework to enable more innovative and accurate diagnosis within the public and private setting.

AI and Machine learning will now augment breast screening and genomic medicine and other aspects of the cancer pathway and for other diseases. Aotearoa will be well along the path of pharmacogenomics and multi-modal analysis. Clinicians will embrace this approach as they will see that the "art of medicine" is now better enabled.

Patients will be better informed and have a greater sense of control of their heath regarding how to prevent what is preventable. Where this is not possible, they will be able to access more precise approaches to treatment. When all else fails they will be willing participants in trials to improve outcomes for the next generation. There is no end game. This is a constant process of innovation and improvement.

Pathway projects for adoption of Precision Health

Genomics

Project 1.Policy Leadership for the introduction of a parliamentary bill to prevent genomic discrimination.

Project 2. Policy Leadership for review and modernisation of legislation relating to gene therapy

Project 3 Policy Leadership for measuring and reporting breast density.

Project 4. Identify and implement budget, systems, processes and capability needed to enable early access to precision medicine and other technologies.

Project 5. Build on and continue to invest in Rakeiora with introduction of a 10K genome project for New Zealand

Project 6. Genomic testing at birth

Project 7. Develop a risk assessment tool for New Zealand (such as CanRisk) with an expectation that risk will be assessed between the ages of 25-30

Project 8. Genomic testing introduced at the time of diagnosis for early and metastatic disease.

Project 9. Continue to research and facilitate high trial participation to differentiate ancestral biological differences from care and social determinants to close the equity gap and to identify new biomarkers and opportunities for intervention.

Pharmacogenomics, to multi-omics and infrastructure

Project 10. Develop PDEs as a clinically relevant model to investigate patient-specific drug responses.

Project 11. Partner and collaborate locally and globally for analysis of tumours and the tumour microenvironment to determine genomically targeted medicine.

Project 12: Collaborate to develop genomically targeted immunotherapies and CAR-T therapies

Project 13: Develop multi-omics ability.

Computational Pathology (CPath) and Computational Radiology

Project 14: Develop (CPath) tailored to our population and within an appropriate ethical framework.

Project 15: Use of AI in breast screening to augment current screening methodologies with a broader concept of risk.

Precision health now and in the future

- Do you think precision health is a worthwhile topic to explore in our Long-term Insights Briefing? Why or why not?

Precision health is certainly a worthwhile topic to explore in a government briefing to develop a future where the health of our population is optimised and our people live long and productive lives.

In the "Long term Precision Health Briefing: now and in the future" request for submission there is a concerning indication of a focus on precision health as distinct from precision medicine.

We see precision medicine as an integral and essential element of precision health. Without the ability to treat precisely and effectively, deep knowledge of an individual's genome cannot lead to transformative outcomes. Separation of precision medicine from precision health in development of the briefing document will leave crucial gaps in the ability to use knowledge gained from genomics. We urge the project team to bring a balanced approach across both elements in their thinking and policy development. Integrated thinking will lead to synergistic advancements within the various elements of precision health and precision medicine. Ongoing research and clinical trials are essential for progress.

We see these issues as highly relevant to New Zealanders health outcomes and welcome this opportunity to explore them in the near and longer term.

The Te Manatū Hauora website advises that "long term insights briefings are used to enhance public debate on long-term issues and usefully contribute to future decision making – not only by government but also by Māori, business, academia, not-for-profit organisations, and the wider public with consideration given to communicating and promoting their findings." [8.]

The timeframe however is confusing as aspects of precision health and precision medicine are available today, sometimes within the public health sector although more frequently within the private sector. Likewise, through research and clinical trial activity, although within New Zealand to a more limited extent. Is this why there is reference to now and in the future?

Irrespective we do see considerable benefit in understanding the current state as well as the nature of issues requiring future focus and resolution for improved clinical outcomes.

We welcome the opportunity to better understand these issues and what is impeding or may impede our progress. It is important we share a common understanding and engage in discussion so that as precision health and precision medicine progress we add value to our health system.

We agree there is a need to explore issues that are known but haven't received adequate consideration to date, as well as new and emerging issues, while acknowledging precision health and precision medicine are with us today.

Benefit will be gained by ensuring issues are:

- better known and understood by a wider audience
- strategies to address barriers enabling progress at a legislative, policy, leadership, cultural/ diversity, operational, technology and infrastructure level including funding to build capacity and capability

- research and clinical trials will provide a pathway to gain access to precision medicine as we build our understanding and provide validation when necessary for our population
- There must be a willingness to translate knowledge to standard of care when benefits are evident.

We will share case studies relating to breast cancer as that is within our knowledge and expertise as consumer advocates. We will on occasion speak more broadly.

Why is this important?

Cancer is the leading cause of health loss and death in Aotearoa New Zealand with approximately 25,000 people diagnosed every year and 9,000 dying.

Te Aho o Te Kahu [9] has said that with stronger prevention measures, up to half of cancers diagnosed every year could be avoided.

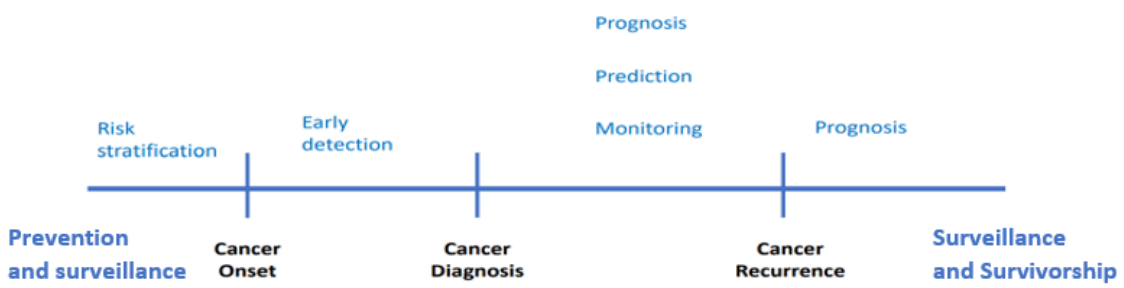
Prevention comes in two forms: *reducing the incidence of cancer* and *reducing late diagnosis* to ensure that the cancer is less likely to recur. Both forms of prevention are critical to precision health, however different cancers present different opportunities for prevention whether they be behavioural or biomedical in nature.

Breast cancer has an overall survival of 89% at 10 years, however 20-30% of breast cancers recur or become advanced, sometimes up to 20 years or more following diagnosis. Some subtypes have poorer outcomes and we know that after adjusting for age, wāhine Māori are 33%, and Pacific 52% more likely to die from breast cancer than New Zealand European, while despite high incidence and late-stage diagnosis, survival is higher in Asian women. Breast cancer is the biggest cause of death for New Zealand women under 65 years of age.[2]

These numbers are unacceptable.

There is an opportunity to bring about transformative change in prevention, early detection, improved diagnosis/prognostics and treatment, quality of life and survival through greater precision across all aspects of the pathway.

Precision health and precision medicine across the breast cancer pathway

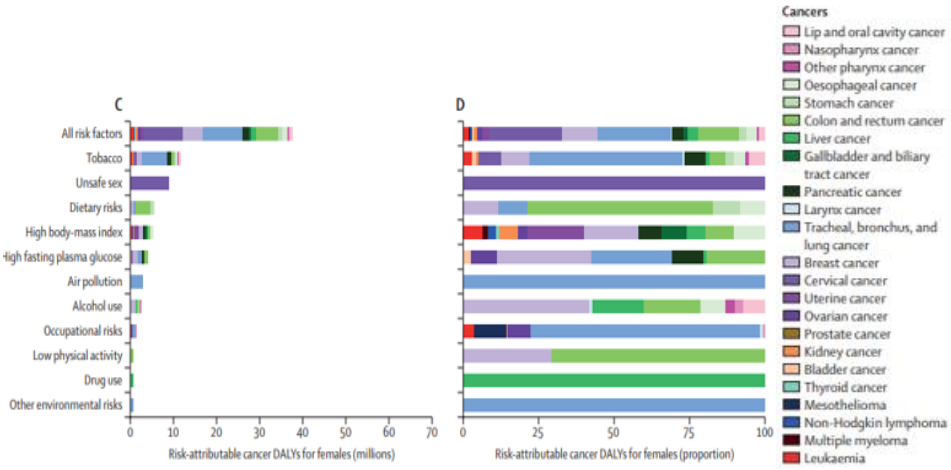


"Statistical considerations for precision medicine" San Antonio Breast Cancer Symposium 2022, Clinical Research Workshop, 6-10 Dec, 2022.

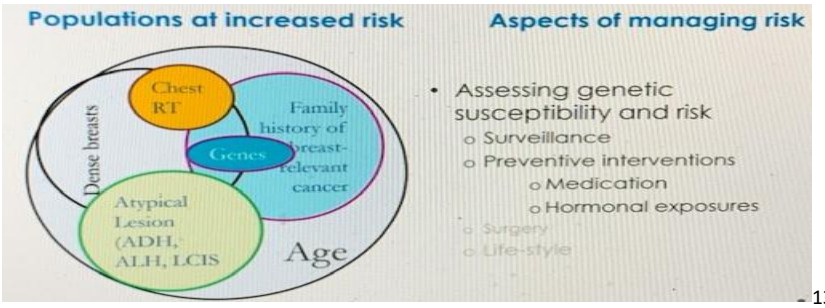
Importantly the diagram above [10] does not indicate a division between precision health and precision medicine. There is a continuous feedback loop, driven by ongoing research and clinical trials, back and forth across the cancer continuum.

The leading risk factors contributing to cancer burden globally were behavioural (2019), and metabolic (2010-2019). Reducing exposure to modifiable risk factors would decrease cancer mortality and Disability Adjusted Life Years (DALYs) however for those whose cancer is less driven by these risks it is vital that cancer risk reduction efforts are **coupled** with comprehensive cancer control strategies that include efforts to support early diagnosis and effective treatment with policies tailored appropriately to local cancer risk factor burden.[1]

Below you can see that for breast cancer lifestyle risks can be narrowed to diet, exercise, BMI, and alcohol consumption and risk reduction efforts in the form of health promotion and education need to be context specific, alongside biomedical factors such as timing of first birth and lactation length.



Breast cancer prevention through tailored education regarding modifiable risk-reduction strategies for example encouraging lactation, avoiding obesity, encouraging high fibre diets and limiting alcohol intake and being active are foundational however they must be coupled with and implemented alongside early-detection and tailored therapy programmes. [11,12]



[13]

For these reasons we agree there is a need for health promotion and education but we also seek equal emphasis on introducing new tools to enable prevention and to facilitate risk assessment and stratification to prevent cancer developing and to reduce late-stage presentation.

We are on the cusp of seeing a growing range of tools from cfDNA[3] to predict risk, to BOADICEA and IBIS[4,5] (which include family history, lifestyle/hormonal risk factors, common genetic susceptibility variants, and mammographic density combined to improve breast cancer risk predictions) to stratify

risk and ctc, ctDNA to diagnose, prognose and monitor risk for early detection and surveillance guidance. [6,7]

Such models will better inform patient, whānau, clinician and community decisions regarding who is at greatest risk and who will need surveillance and tailored screening and in addition those at low risk who may need less follow up. [14]

Importantly, precision will reduce the number of patients being treated with medicines that will not benefit them.

In New Zealand we see too many Māori, Pacific and Asian women diagnosed late stage [9]. For breast cancers diagnosed as early-stage, treatment is more effective and affordable, better tolerated, and practical to administer in restricted-resource environments.

Evidence tells us improved early detection requires multiple coordinated interventions. All are required to facilitate growing opportunities to predict, prevent or promptly refer those at increased risk of presenting with early breast cancers for adequate diagnostic evaluation, particularly for younger and older women within our communities.

In addition, new trials demonstrate that those with high-risk *early breast cancer* need closer monitoring of their residual disease, with time of the essence to guide effective therapy. [15]

Those with metastatic breast cancer who are HR+ HER2 negative today will not have their treatment resistance monitored, learning only when the cancer has further advanced and symptoms appear. Increasingly we can demonstrate that there is an advantage from ctc, ctDNA monitoring to gain an early indication of resistance and its nature so that there is a chance to treat resistant mutations more precisely e.g., ESR1 (wild type and endocrine driven), AKT, PIK3CA/mTOR or PARP.

ESCAT approvals are increasing in line with targeted therapy for these mutations. Continuing to treat these patients with endocrine therapy alone is not precision health nor precision medicine. Quality of life, impact on whānau and the impact of metastatic disease all need to be recognised.[6,7]

Those with breast cancer therefore require timely access to stage-appropriate, multidisciplinary cancer treatment (i.e., surgery, radiotherapy, and systemic treatment), through which locoregional disease is controlled and metastatic progression is avoided.

Comprehensive, person-centred care is required from the beginning of therapy to multimodality treatment completion and rehabilitation survivorship and palliative care support as part of an integrated care model. [16]

- What opportunities does precision health create for more effective health care in the future (more than 10 years ahead)?

We see opportunities leading into and more than 10 years as follows.

New Zealand has moved from a dedicated Population Health approach to Precision Health through innovation, funded access to new technologies validated on our population and through increased participation in research and clinical trials

- Policy leadership has helped put in place broad and simple legislation to prevent genomic discrimination.
- Policy leadership has initiated a risk focussed regulatory review of lab-contained, biomedical applications to better enable gene therapy research.
- Policy leadership has enabled reporting of breast density to better inform patient decisions
- Policy issues relating to Te Tiriti o Waitangi and data sovereignty are resolved, governance and the necessary protocols are well established and socialised
- New Zealand's 10,000 Genome project is in place, well governed and with the necessary infrastructure through broad health system and scientific collaboration. Data is safely provided for ongoing research and clinical trial access is available to many
- Risk assessment and stratification will have a level of sensitivity and specificity suited to our unique population (Māori, Pacific, Asian, other nationalities and European New Zealanders) covering a broad range of risks which have been well validated through genomic research and clinical trials. Levels of concordance will be known and understood and new biomarkers developed to meet our diverse population needs.
- Tools utilised include modified BODICEA/IBIS and cfDNA
- Risk assessment will be completed at birth and age 30 (or younger if risks are known) on a voluntary basis so that preventative strategies may be developed. Information sharing and education occur through counselling alongside provision of corrective, preventative and or surveillance measures.
- Information regarding behavioural and biomedical risks will be readily available to people within their communities and programmes will be in place for those wanting to actively modify their risks based on what they have learned. Information will be both generic and targeted and risk differences among cancers and across diseases will be acknowledged.
- The spontaneous nature of some cancers and diseases will be understood and acknowledged.
- Risk assessment will be improved through local AI and machine learning data which will have raised sensitivity and specificity of screen detected cancer to facilitate early and accurate detection. This has supplemented and improved our radiographic resource availability e.g., no unwarranted reading required for low-risk individuals.
- Liquid biopsy as a means of detection will be integrated into clinical practice for prediction, prognostic purposes, monitoring and surveillance.
- Locally validated and culturally appropriate risk assessment will have been successfully integrated into community services, primary care and secondary care and direct to consumers with guidance available locally or online, through nurse coordinators and specialist counsellors to support this approach. Through this process individuals have access to ongoing education about their risks.
- Those at low risk may choose to participate in screening less frequently.
- Those at above average or high risk will have ease of access to surveillance. Trade-offs will be communicated and understood.

- Access, intensity and modality of screening will be based on risk and tailored to ensure early diagnosis (preventative against metastasis)
    - Modelling will have been done to validate the cost benefits of screening Māori, Pacific, Asian and high-risk New Zealanders at a younger age to ensure early diagnosis
    - more frequent and or supplementary screening will be provided when indicated to ensure early diagnosis.
    - breast density will be measured, reported and accepted as a risk factor alongside other risk factors as it masks mammographic breast cancer and is an independent risk factor
    - The precision of this system refreshes constantly through research and clinical trials and frequently refreshed guidelines
- Prevention: Biomedical interventions have been trialled and there is regular introduction of new inhibitors/modifiers of risk in place of surgical options especially for younger patients
- Well governed and monitored infrastructure will support this approach. This will recognise Te Tiriti o Waitangi and manage data sovereignty issues relating to storage and access issues for, tissue, microbiome, or other bodily fluids
- New Zealand will have further developed its bioinformatics and computational capability
- Genomic counselling will be mainstreamed across all hereditary syndromes or available online
- Online specialist support will be available but not centrally located
- Late-stage diagnosis occurs infrequently
- Those at high or moderate risk of disease have been identified and are monitored
- Capacity, capability and new technologies and medical devices support those under active surveillance on the precision health pathway. This approach is funded
- Health economics and modelling have assisted policy makers to transition resource to support early diagnosis and intervention. It is now recognised investment up front is beneficial to the system as a whole and importantly the quality of life and wellbeing of individuals and their families through prevention of longer-term illness and mortality.

New Zealand has moved to a Precision Medicine approach through innovation and funded access to new technologies and increased participation in research and clinical trials

- Computational pathology (CPATH)/computer assisted computer algorithms aligned to an agreed ethical framework has been developed to provide novel approaches to diagnosis and assessment and to facilitate speed of patient clinician decision making
    - It has improved productivity in pathology and provided fast access to detailed diagnostic results
    - Significantly more detailed clinical information is now freely available within the public system from genomic to validated biomarker data
    - Communities have been consulted regarding this change. The ethical and cultural aspects have been addressed and there has been significant support for implementation in Aotearoa
    - Research has been concluded and clinical trials are ongoing alongside this implementation
- In an extension to the 10,000-genome project New Zealand has Genomic Medicine partnerships which enable immunotherapy and vaccine developments suited to our unique population

- Guidelines have been developed across cancers and disease types regarding well validated treatment algorithms as defined in international guidelines such as NCCN and ESMO (in line with New Zealand's ESMO, ESCAT model)[7]. These are regularly updated to ensure treatment protocols are optimised
- Personalised New Zealand explant and organoid libraries based on our population by disease type enable treatment protocols to be tailored based on real-time high-quality information
    - Progression is rapidly responded to via pharmaco and multi genomic analysis and ESCAT algorithms of funded treatments made available to the smaller number of patients with advanced disease who will benefit
- De-scalation and escalation of treatment is made possible through use of medical devices (digital health) and assays validated for our population for surgery, therapy and radiotherapy
    - Assays and clinical pathological information provide clinicians and patients the information required to make informed decisions with clear decision aides
- Surveillance of patients is via ctDNA and ctc's and through equitable access to imaging technologies such as radiomics
- Overall survival, progression free survival and quality of life are monitored and analysed through clinical trials to improve precision
- Survivorship programmes are tailored to the needs of patients and monitored as necessary
- Palliative care is an integrated aspect of this system but less in demand for cancer as most diagnoses are early-stage disease.

- ## What barriers or restrictions do you see in the health system that might hold it back from adapting future precision health advancements?

Barriers we perceive relating to the above initiatives.

The need for Policy Leadership regarding genomic discrimination

New Zealand has failed to put in place protective mechanisms to minimise genomic discrimination. This enables insurance companies, employers and others to use information from genomic testing to restrict the rights and entitlements of people and their whānau and creates a disincentive to test and gain valuable genetic information that can allow early and effective medical intervention for a range of conditions.

Prof. Andrew Shelling et al, University of Auckland, "Genomic discrimination in New Zealand health and life insurance (AGenDA)" highlighted this issue with a paper published in the New Zealand Medical Journal.[17] AGenDA made clear there is substantial public benefit from encouraging people to take genetic tests on the basis genetic information is used to:

- facilitate the early detection of illnesses and improve the opportunity to achieve better health outcomes, including through earlier preventative interventions and/or targeted therapy
- develop more effective, and less harmful, medicine and therapy; and
- aid research of disease

This was highlighted by Laura O'Gorman KC, in her paper titled, Genomic Discrimination - the need for a legislative response, October 2022. Laura O'Gorman proposes a legislative response (Appendix 1) to resolve this issue.

New Zealand sits separately from other OECD countries in the absence of protection against genomic discrimination and in its absence people and their whānau are being impacted.

Outside of New Zealand this issue has been managed by specific legislation or self-regulation (industry codes/moratoria). Within New Zealand nothing currently in place prevents private service providers, such as insurers, from asking for and using genomic test results and using that information to refuse access to services, or to charge more for them (e.g., higher insurance premiums).

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 (focussed on individual entitlements) are inadequate to protect:

- health information as regarded as a taonga (treasure) that must be cared for, used and
- treated with respect; and
- genetic information is viewed as collective (rather than individual) property, since it carries information about whānau, hapū and iwi (both historical and current/predictive).

The Universal Declaration on the Human Genome and Human Rights was adopted unanimously in 1997 and endorsed by the General Conference in 1999. Article 6 provides: No one shall be subjected to discrimination based on genetic characteristics that is intended to infringe or has the effect of infringing human rights, fundamental freedoms and human dignity.

In responding to these commitments and genomic discrimination, the United Kingdom, Canada, US and Australia have all responded to the need for protection by legislation alone or in combination with moratoria.

Of the range of options, the general Canadian legislative approach appears the most attractive with its breadth, clarity and simplicity and we hope will lead to similar legislation within New Zealand.

Recent conversations with Jane Tiller, Ethical Legal & Social Adviser - Public Health Genomics, Monash University, Melbourne and Senior Project Coordinator, Australian Genomics has made it clear that Australia's moratorium is inadequate, it was always seen as a temporary measure and there is an intention for Australia to now move towards legislation.

Fay Sowerby, Secretary BCAC and Chair, Breast Cancer Cure has worked alongside Prof. Andrew Shelling, Associate Dean (Research), Faculty of Medical and Health Sciences, University of Auckland for the for the last three months approaching government organisations and insurers to better understand these barriers. This work is not complete but there are early indications insurers prefer legislation over a moratorium. **Government organisations must step up and provide policy leadership on this issue**.

Three aspects are required to make progress: Policy, Legal and Communications Media.

AGenDA through pro bono support have the latter two in hand, we do however need policy leadership and we will continue to seek further feedback in 2023.

The New Zealand Law Society Health Law committee have asked Laura to assist them with an issues paper for the Law Commission as a piece of legislation requiring focus (it will sit alongside other issues). They will determine priority.

Fay and Andrew have approached Richard Klipin CEO Financial Services Council of New Zealand with the objective of seeking his assistance to bring New Zealand in line with other jurisdictions.

It is our view that legislative change would assist the insurance industry and New Zealand consumers in reflecting the global reality and achieving societal equity.

We have enquired about the Insurance Contracts Bill (this sits with MBIE currently) as a possible path. Insurers see the passage of this bill as too advanced to try and introduce an entirely new concept that would only complicate things further and they don't think we will succeed for this reason alone, putting aside other issues. We continue to seek feedback from MBIE themselves. Liaising with Gary Evans, Chief Science Advisor, MBIE).

We and other AGenDA members have liaised with Chief Science Advisor, Professor Dame Juliet Gerrard, the Human Rights Commission, legal counsel John Hancock and the Privacy Commissioner who will not lead on this issue and just wish to be kept informed.

Fay, Andrew and Laura are continuing to look at the Human Rights legislation relative to the exception clause for insurers enabling discrimination on the grounds of health status (Bill of Rights) where increased risk/likelihood to claim is supported by actuarial data (and the degree of evidence such data provides) through a discussion planned with Paul Rishworth KC, author of the Bill of Rights legislation.

In addition, we intend to explore the Financial Markets Authority Conduct of Financial Institutions (CoFI) legislation. The Financial Markets (Conduct of Institutions) Amendment Act 2022 amends the Financial Markets Conduct Act 2013 to ensure financial institutions treat consumers fairly. It is designed to protect consumers by putting the consumer at the forefront of institutions' decisions and actions. Also known as the Conduct of Financial Institutions (CoFI) legislation, it introduces a new regulatory regime to ensure registered banks, licensed insurers and licensed non-bank deposit takers comply with the fair conduct principle when providing relevant services to consumers. It is important that consumers get the financial products and services they need throughout their life, when they need them, and have trust and confidence these will deliver what is fair and reasonable. CoFI significantly expands the FMA's mandate as a conduct regulator to include financial institutions, and confers new responsibilities in terms of licensing, monitoring and enforcement.

We have also liaised with Te Aho o Te Kahu who have asked to be kept informed.

There are people who have completed and are completing their PhD dissertations on this issue and there are highly motivated iwi Māori and Pacific communities following this issue with concern and interest.

To better understand the insurer perspective, we have spoken to insurers. We have determined that one would not discriminate while others would in the context of extra cancer cover where they may gather information regarding genetic test results, hereditary conditions and family history, which may result in amendment to the terms of cover offered.

This barrier has been removed in the UK, Canada, the US and Australia and urgently requires attention in New Zealand. It will remain a barrier until a government organisation steps up and leads on this issue. In the interim it will deter people from more personalised care (Precision Health/Precision Medicine) which will negatively impact the health of New Zealanders, in particular our Māori and Pacific populations, while the status quo remains.

A need for Policy Leadership regarding gene therapy

New therapies involving revolutionary gene-editing technology CRISPR-Cas9 will increasingly offer permanent cures for rare but debilitating genetic hereditary disorders. While New Zealand's strict regulations around genetic modification have made it difficult to carry out gene-editing research in humans, there have been several medical trials launched. The Auckland Clinical Immunologist ***Hilary Longhurst*** who led the local world-first trial targeting hereditary angioedema (HAE), sees potential for the cutting-edge techniques to be turned against a raft of other genetic disorders. The effect of treatments is to silence (rub out, cut out) faulty genes through a growing range of techniques to prevent/stop conditions. Examples globally include Sickle Cell disease (US), childhood blindness (UK), cystic fibrosis and haemophilia and there is now promise for more complex disorders such as heart disease, cancer and HIV. The recent trial in New Zealand required just a single treatment. Longhurst says there is "huge potential" for development of similar CRISPR-Cas9 treatments for other genetic disorders. "I think we're at the dawn of a new age of treatments where, if we can pinpoint the gene, we might be able to sort out the problem in a single treatment ... it's really exciting to be a part of".[18]

Of note the first gene therapy for treating high-risk bladder cancer that has not invaded muscle recently won FDA approval.[19]

Last August, Carvykti, a treatment in which a patient's cells are taken and modified to create cancer-killing Car-T cells, before being reinserted to become living drugs, became the second-ever GMO to be approved for uncontrolled release in New Zealand.[18]

A research project in New Zealand led by Vanessa Lau (UoO) seeks to inhibit the BRCA2 gene in breast cancer through antisense oligometastatic nucleotides to eliminate this high-risk variant by gene splicing, this team are working in collaboration with those bringing a similar focus to Huntington's disease.[20]

We in New Zealand need a regulatory review focused on such lab-contained research, with biomedical applications that considers risk and benefit rather than focusing specifically on the GM technology involved.

A lack of funding and resource constraints (capacity and capability) preventing a move towards precision health/medicine best practice standards being applied.

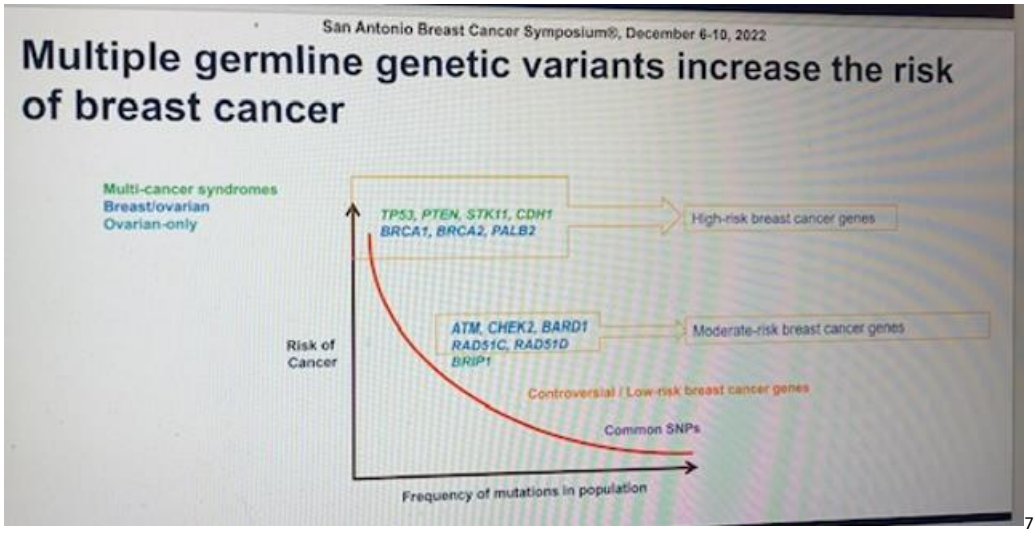
To provide an understanding of how limited resource is impacting our health outcomes and an ability to bring precision health/medicine benefits to New Zealanders we will focus on the moderate risk pathway.

Genomic testing pathways for New Zealand breast cancer patients need to be adequately funded and optimised to reduce the impact of hereditary cancer syndromes for individuals and their whānau, by reducing barriers to entry to increase precision and prevent late-stage diagnoses.

The landscape for high and moderate risk genes is shown below and is relevant to breast and ovarian cancer. The pathway in New Zealand is clear for those with high-risk prevalent genes but for

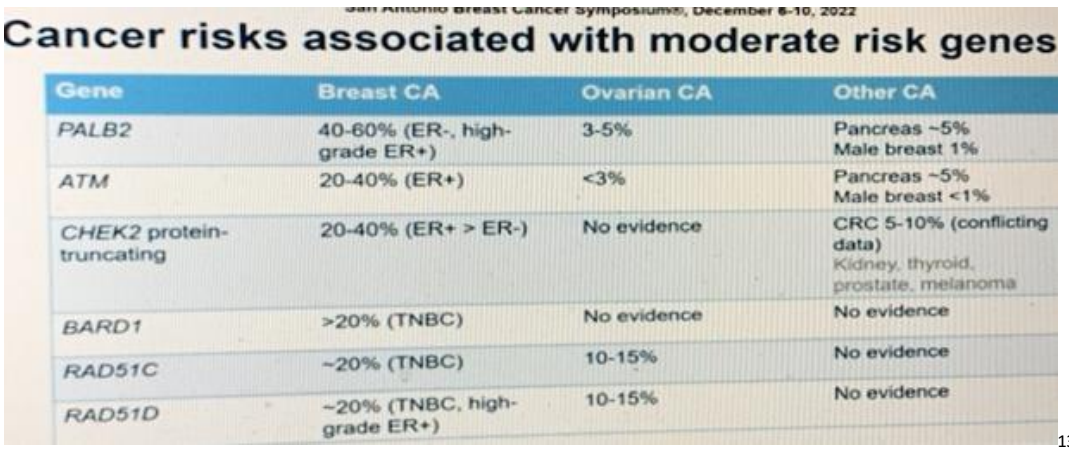
those who fall in the moderate risk group, the pathway is broken following the withdrawal of services by Genetic Health Services NZ (GHSNZ). [21]

This stance, which has been taken specifically to reduce workload, lowers standards of care. Withdrawl of these services will favour those who proactively seek or pay for support, increasing inequity of care.



[7]

Pathogenic variants in breast cancer such as BRCA1, BRCA2 and PALB2 account for the majority of hereditary breast and ovarian cancer cases in individuals with a strong family history or early onset diagnosis. They are however not the only genes associated with hereditary breast cancer. Other cancer syndromes like CDH1, PTEN, STK11,TP53, and breast cancer moderate risk genes like ATM, CHEK2, BARD1 and RAD51 C and RAD51 D may also influence risk for breast and other types of cancers.[22] The inclusion of these genes is important because individuals with a pathogenic variant in one of these genes has a *significantly increased risk* of developing cancer and these cancers may be difficult to detect and treat. Identifying these genes may also result in risk reduction and early diagnosis of other cancers following cascade testing within a family, increasing the chances of successful treatment and survival. Although those with a genetic variant have an increased risk of developing the disease[23-25] an additional 20 percent will have a close family member who also had breast cancer, suggesting a familial link even though no specific genetic variant may have been identified.[26] In this case, cancer surveillance recommendations are based on personal and family medical histories. This is precision health.



Gene	Breast CA	Ovarian CA	Other CA
PALB2	40-60% (ER-, high-grade ER+)	3-5%	Pancreas ~5% Male breast 1%
ATM	20-40% (ER+)	<3%	Pancreas ~5% Male breast <1%
CHEK2 protein-truncating	20-40% (ER+ > ER-)	No evidence	CRC 5-10% (conflicting data) Kidney, thyroid, prostate, melanoma
BARD1	>20% (TNBC)	No evidence	No evidence
RAD51C	~20% (TNBC)	10-15%	No evidence
RAD51D	~20% (TNBC, high-grade ER+)	10-15%	No evidence

[13]

Results from a New Zealand study (Vanessa Lattimore et al, September 2020)[27] show 3.5% of breast cancer patients carried a pathogenic or likely pathogenic variant in *BRCA1*, *BRCA2, PALB2*, or *PTEN*. A significantly higher number of pathogenic variant carriers had grade 3 tumours (76%) when compared to non-carriers. That is why it is important they are identified and receive surveillance early.

From the same study we learn that notably, 46% of the identified (likely) pathogenic variant carriers had not been referred for a genetic assessment and consideration of genetic testing. This study shows a potential under-ascertainment of those carrying a (likely) variant in a high-risk breast cancer susceptibility gene.

Dr Mary Claire King renowned American Geneticist[28] made it known at SABCS 2020 that 50% of patients with no family history have completely preventable cancer (transferred from fathers and therefore not obvious). She went on to stress that every breast and ovarian cancer patient with a mutation detected after diagnosis is a missed opportunity to prevent a cancer and that no person with a recognised mutation should die from breast cancer.

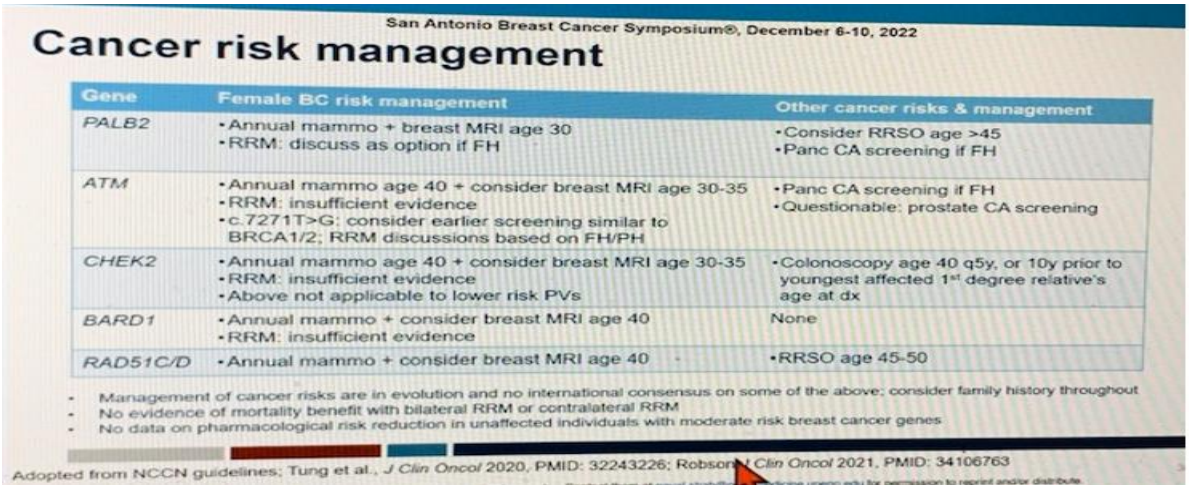
For those who do test positive for a high-risk gene or whose family history is obvious, the pathway is clear. A definition of high risk of breast cancer immediately removes these individuals from the BreastScreen Aotearoa programme.

For some however it is not so easy.

Those deemed at moderate risk when they present to GHSNZ who will have previously warranted surveillance and support, today **with resource constraints** are advised of their moderate risk status **by letter** with further follow up and support left to their primary care provider or private clinic should they be able to fund this. Genetic counselling is not provided. Without a means of tracking those at moderate risk over time, they are at risk of being lost to the system.

While John Fountain, Manager, Data, Monitoring and Reporting Data, Monitoring and Reporting at Te Aho o Te Kahu speaking at a Familial Breast and Ovarian Cancer meeting in August 2022, [29] has made it clear that there will be a process to do this in the future, immediately it is not a priority. We hope in 2023 it will become a priority as an inability to track these cases will lead to greater disease burden for individuals and whānau and ultimately cost the health system more. We are concerned that there is no process in place for surveillance and support for this group. There will be some who will be proactive but many will not, particularly as time progresses. There is therefore a potential risk that this group and their families will be at risk of a late diagnosis that will likely result in advanced breast cancer. This is NOT precision health.

Multiple hereditary cancer genes that contribute to breast cancer risk are now well-characterized and included in widely available multigene panel testing. Moderate-risk genes are associated with a 1.5- to 3-fold greater incidence of lifetime breast cancer in affected individuals than in the normal population, which stands at about 12% to 13% incidence over a lifetime. Current NCCN guidelines recommend increased surveillance of individuals possessing a pathogenic variation in ATM, CHEK2, and PALB2. More liberal use of MRIs, starting with a baseline exam at age 30 to 35 years, should become part of the standard approach to monitoring individuals found to have an alteration in these genes. For moderate risk genes, MRI added to annual mammography at age 40 reduced mortality by greater than 40%, MRI at 30-35 and mammography at 40 balances risks and benefits. [30] Below are adaptations to the NCCN guidelines for moderate risk genes (this work was done prior to PALB2 being recognised as high risk).



13

Genomic testing provides an explanation for your personal or family history of cancer, evaluates your risk of developing future cancers, and will help inform medical decisions, including treatment, surveillance, and preventive options and enable participation in clinical trials or research studies, and will also identify other at-risk relatives for whom genetic testing is recommended.

Our concern is that without adequate resources and systems in place to support this form of risk assessment a form of triage is being used, the Manchester score (MSS3). Anyone over the age of 62 will be highly unlikely to be able to access GHSNZ and therefore be precluded from being genetically tested.

Why are GHSNZ restricting those they test?

They say that servicing the moderate risk patients would double the number of patients seen which would result in restricted access for unaffected patients with family history. Resource constraints rather than best practice are driving the system.

This is an example where a lack of funding and resource capacity and capability to support surveillance may be a poor form of efficiency as it will cost our health system more in the long term as late-stage patients become advanced with a need for therapy over prolonged periods and suffer shortened lives, not to mention quality of life impacts for these patients and their whānau.

It is easy to understand why this is happening but the implications are concerning especially when criteria used to determine who should be tested may be perceived as lacking the necessary rigour and sensitivity we would expect today. Yadav et al, Clinical Oncology, 2020, [31] found that generally criteria used are insensitive for detection of pathogenic variants. Criteria were generally put in place when testing was expensive and slow. Globally that is no longer the case and yet in New Zealnd we continue to impose these restrictions because of resource and funding constraints.

We are concerned that in New Zealand we seem determined to restrict who can "seek" value from this taonga.

At a recent Breast Cancer Trials Q&A, *Breast Cancer & Genetics webinar* (October 2022) Prof. Geoff Lindeman Joint Head ACRF Breast and Stem Cells, Walter and Eliza Hall Institute [32], said "we are gradually **moving away from thresholds and broadening the range of people we test.** The cost of tests is now somewhere between $300AU and $500AU and it is seen as a strong preventative

measure for those who do not have a clear family history or when there are many men in the family and the family history becomes less clear".

At what point will New Zealand move towards genomic testing and begin to recognise that this is a preventative precision health strategy that will positively impact our mortality statistics? Countries such as the UK and Australia understand the value provided by genomic testing and are assertive in its use as well as the guidance and support required.

Funding for the storage and use of large-scale data which improves health equity and respects data sovereignty.

We wish to highlight Professor Cris Print's comments when he spoke at Clinical Trials NZ meeting in 2022, [33], "Genomics is seen as the new horizon within which lies ground holding treasure." "Precision oncology data is a unique type of patient data that is rapidly growing in complexity and impact. It is used both for the clinical care of current patients and for research to improve the care of future patients. The challenge is in how to store and use precision oncology data, linked to clinical data, in a way that is safe, secure and effective, furthers health equity, is co-governed with Māori, and respects Māori data sovereignty.

The Rakeiroa initiative believes that precision oncology data and the associated technologies have the capacity to mitigate cancer outcome inequities in Aotearoa providing there is a national strategy, which is equity-led, has national funding, collaboration and co-governance with Māori. Future considerations include the need to identify potential partnerships and funding sources, with potential collaboration from a wide range of sectors" This work is critical to precision health and precision medicine. They are co-developing innovative scalable national genomics research infrastructure to manage and govern data, its ownership and guardianship, including New Zealand-specific genomic databases. This will enable researchers to translate genomic knowledge into health practices that advance the wellbeing of New Zealanders, and in particular address the country's health inequities by developing genomic tools that put the needs and priorities of Māori, at the centre. [34] They aim to ensure genomic data is collected and used appropriately to benefit all New Zealanders, especially Māori and Pacific peoples, including people with cancer. By co-designing and co-governing this genomic data analysis with Māori colleagues, there is an intention to reduce health inequities.

The programme encompasses two medium-scale research projects giving representation of health and genomic data to two ends of the spectrum – rural Tairāwhiti (East Coast) and urban Auckland, and primary care and tertiary care (tertiary care is specialised consultative health care, and in this project has a cancer focus) – as well as the opportunity to work with Māori, Pasifika and Pākehā.

- Genome sequences from hundreds of individuals co-led and co-governed with Māori and stored securely but accessible for ethically approved and consented research
- Data linkable and protected with careful governance and approval to primary and secondary care health data and National Health Datasets
- Recommendations for process scale-up
- Knowledge on how to apply research for health benefits

We respect this work and want to better understand how and when translation into secondary care will happen and integration with the CAN Share project occurs. We suggest that this project warrants ongoing investment.

There is a need for consumer and community education and socialisation regarding these issues so that people may understand the positive outcomes to be gained from genomic testing and precision health, while being realistic that some may gain more than others. Legislation to protect against discrimination is vital.

We want to see these projects leveraged in line with a New Zealand version of the Genomics UK 100, 000 Genomes project, possibly titled the 10K Genomics NZ programme.

Risk prediction and stratification tools critical to precision health have not been validated on our population and guidelines to support changes to clinical practice are not in place.

Risk stratification models such as BOADICEA (CanRisk) [4] and IBIS (Tyrer Cuzik) [5] are both in limited but increasing use in New Zealand. They provide a more precise estimate of lifetime risk allowing for reclassification of some individuals as having low or population risk. They also allow for more precise age specific estimates of cancer risk, thereby impacting the age at which high risk breast or ovarian screening begins (although this may also be dependent on guidelines currently in use). To improve fit for our population 4 issues, need to be addressed.

- These tools need to be validated in our population. They have been validated on mainly European populations rather than diverse ancestry groups e.g., Māori, Pacific and Asian.
- Few younger women took part in the original trials and therefore it is thought lifetime risks are regarded as less accurate in young women (Robert J MacInnis, JNCI, 2021). [35]
- In New Zealand we neither report nor measure breast density, CanRisk and IBIS incorporate breast density but local guidelines do not suggest any change to clinical practice. Benefits available from the tool are lost as differing surveillance and modality recommendations are ignored. [36]
- Funding is not available to customise tools to ensure their look and feel is inclusive of the entire population, in order to encourage participation.

The Canterbury Initiative [37] – has been trying to provide GHSNZ with better information for the moderate risk pathway utilising CanRisk, an online tool to assess risk. In some instances, this has been done in primary care however it is mainly administered by a CanRisk nurse alongside a patient (online or by telephone). This tool is used to assist women and their GP by providing additional information prior to engaging with GHSNZ.

The team reviewed the programme between April 21 and January 22. Moderate risk was determined by CanRisk, GHSNZ or Breast Multidisciplinary meeting assessment (MDM). Of those evaluated 2% suggested high risk (based on Lau et al, 2020 this appears light), 71% moderate risk and 27% population risk. These figures are informative in telling us the size of the moderate risk population. The team want to understand where CanRisk sits in the system. They have also expressed concern regarding variability across the funded at-risk screening pathway.

The team have questioned whether lifestyle factors should be incorporated in CanRisk assessments as they have focussed on familial and not lifestyle factors.

- *We highly recommend lifestyle factors be incorporated. It is by combining risk factors including, familial, SNPs, breast density and medical we fully understand risk. For example, if post-menopausal women with high BMI and younger women with high levels of abdominal fat and either group being sedentary along with alcohol consumption, low fibre diet and smoking with moderate risk genes, would immediately impact their risk score.*
- *Breast Density has also not been incorporated and we know this can create an increase of 2.1-4.6x* [38]*. They acknowledge this would be easy as most mammograms today provide a*

reading and can be readily reported. Breast density reporting and incorporation brings value beyond extending the period of screening e.g., lowering the age to 40 for some. Breast density risk not only increases the risk of breast cancer, it also masks breast cancer on a mammogram and as a result increases the risk of late-stage diagnoses and interval cancers. Recommendations for more sensitive modalities for some is also important and its incorporation alongside other risk factors will provide a more accurate risk score.

- *There is a bias towards those who know and understand their family history.*
- *These tools have not been validated for our non-European population.*

Risk stratification relating to Ancestry and Breast Density: To prepare for risk stratified screening it is important that research occur to better understand the implications of Single Nucleotide Polymorphism's (SNP's) for non-European New Zealanders. For example, only 39% of SNP's identified in European women are replicated in Asian women.[38]

Risk Stratification to assist modality selection: Locally in recognition of stratified risk Dr Sugania Reddy Specialist Radiologist Mercy radiology is leading a trial with Southern Cross https://radiology.co.nz/news/new-breast-imaging-pathway-a-pilot-between-mercy-radiology-and-southern-cross investigating the use of IBIS (Tyrer Cuzik risk assessment), without the SNP element to stratify risk to determine the benefit of providing differing modalities to optimise their screening programme. [38] This pilot is said to be necessary to justify supplementary screening for those at higher risk including breast density for insurance purposes.

Breast density measurement is driving risk stratified and personalised screening globally. BreastScreen Australia supports discussion and public awareness of breast density and Michelle Reintals Clinical Director BreastScreen Australia has 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. IT implementation, integrating Volpara software was hard but critical. 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 percent were category C (heterogeneously dense) and 7.9 percent were category D (extremely dense) which indicates those with high density were just over 31% and not the expected 50% in the combined higher category. There were variations by site but the pattern was similar. **This study continues as does roll-out. Why such initiatives are important is that we need to understand our population and model how best to provide more precise treatment.** [38]

Find it Early Act: 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. Is such action required in New Zealand to ensure greater precision? The U.S. federal bill, the Find It Early Act, for expanded insurance coverage for no-cost screening and diagnostic imaging for women with dense breasts or at increased risk, can be accessed at DENSE Breast Info. [36]

Prevention and immune signalling: Kara Britt (Peter McCallum Cancer centre) and Wendy Ingman Assoc. Prof. (Adelaide Hospital). 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. [38]

Increased risk of contralateral cancer from mammographic density (MD): Gretchen Gierach, Deputy Chief of the Integrative Tumour Epidemiology Branch in the National Cancer Institute. Gretchen et al researched the relationship between pre and post breast cancer diagnosis measures of MD with contralateral breast cancer risk within a community healthcare setting. 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 BD dropped by 5% or greater the risk declined. This research continues. [38]

Risk Stratification for personalisation: Jennifer Brooks, Assoc Prof. of Epidemiology, DLS Public Health, Ontario described Risk Stratified Screening in the Ontario Breast Screening Program: Aim: to improve personalised risk assessment to offer cost effective risk-based screening and prevention for individuals most likely to benefit and to determine optimal implementation approaches within the Canadian Health System. This is being done in Ontario and Quebec – the target age is those 40-69. They are utilising the CanRisk (BOADICEA) online 10-year risk tool to determine average, higher than average or high risk based on age specific thresholds. They recognise some are likely being over-screened and some under-screened. Half of those being screened annually for breast density are at average risk but 12% are high risk. The results support the need for multifactorial risk prediction. They see value in going beyond family history and density and including PRS based recommendations (Canada have genomic discrimination protection through legislation, we in New Zealand do not).The study is ongoing and risk estimates will be recalculated and psychosocial outcomes evaluated. [38]

Recent Trials driving personalisation including an evaluation of frequency: The US based WISDOM trial (a randomised and adaptive trial incorporating choice). Laura Esserman and Athena investigators established **the WISDOM (Women Informed to Screen Depending on Risk) trial** in the US 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 terms of 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. It is a pragmatic, adaptive, randomized clinical trial comparing a comprehensive risk-based approach to traditional annual breast cancer screening. The multicentre trial which is powered for a primary endpoint of non-inferiority with respect to the number of late-stage cancers detected. They will adapt 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. Esserman et al, 2017) https://doi:10.1038/s41523-017-0035-5. [38]

Likewise, **MyPeBS in the UK** a randomised trial utilising the CanRisk (BOADICEA) tool. This tool is already being utilised by some in New Zealand. The genetic SNP elements are not often used in New Zealand. It has been automated for direct use with consumers via BRRISK and was to be integrated into a Primary Health Care facility to identify breast and ovarian cancer risk. It needs a more culturally appropriate interface to be used by Māori and Pasifika and simplified in terms of who answers which questions. [39]

In the US where the majority of the state's measure and report density, the Society of Breast Imaging (SBI) and American College of Radiology (ACR) Guidelines were updated in February 2020 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. Both groups continue to recommend that women at average breast cancer risk begin screening at age 40. I record this here because it indicates the special status awarded to African American women in recognition of their poorer outcomes. [40]

For precision health and precision medicine to become a reality, risk stratification measures in New Zealand need to recognise ancestral differences, fit effectively into funded pathways and have guidelines aligned to new evidence, without that they will reinforce existing inequities.

Preference for the status quo and resistance to more personalised screening

Is this cost and resource or ideologically driven or is it because it is impossible to complete randomised trials which demonstrate non inferiority of more personalised/precise approaches

The purpose of risk assessment is to guide surveillance to increase the likelihood of early diagnosis or to assist with prevention.

From a policy perspective we seem slow to respond 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). 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. The epidemiologists we meet have ongoing concern regarding over diagnosis from more tailored screening models. This is disappointing and warrants deeper discussion as these initiatives are trying to redress and maintain a balance between over and under diagnosis. As consumers we are concerned that in New Zealand, despite international evidence, the balance is tipped toward a concern for over diagnosis and over screening. We respect that the emphasis should be there but welcome a more balanced approach when reviewing new evidence with an equal consideration for under diagnosis which we believe has serious consequences in the form of late diagnoses in today's less precise environment. To move toward a more precise approach we will have to be more open to new trial options and ways of researching these new approaches in our population. This means identifying under diagnosis as an issue to be addressed.

- **Screening Programme objectives**. The current focus is on mortality and we need a greater focus on issues that will drive more precise and earlier diagnosis. Many women are suited to mammographic screening but not all. To achieve earlier diagnosis, we need to bring an emphasis to interval cancer, late stage/high-grade diagnoses and de novo/advanced diagnoses as lead indicators for the screening programme. Mortality should remain 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 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 look to reduce these impacts and costs. Greater investment at the front end of the system by incorporating risk stratification alongside screening when considering extending the age range, differing modalities

or frequency may look very different. They can be modelled utilising health economics and GIS together with data from the Breast Cancer Registers.

- **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 is delayed, we are impacting lives.
- **Modality:** There are options now available. The population-based model seems to have little capacity or flexibility to test new options and the opportunity to discover different outcomes which may be more cost effective in the longer term is lost. No one modality can provide the answer, it is how we fine tune and optimise systems with the whole picture in mind. e.g., having an ultrasound or Contrast Enhanced mammography (CEM) system on a screening bus in a remote location so that those having a screen or those needing a rescreen particularly those at above average risk or those needing follow up can have access without the need for a visit to a distant hospital. This is 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, an Abbreviated MRI $700-800 and full MRI $2000 approximately. Specificity accrues across this range from 5-7/1000-16.5/1000 respectively. It is through greater sensitivity and specificity we will enter the precision health era. [41]

Prevention reliant on behavioural change and modifiable biomedical risk: Breast cancer lifestyle behavioural risks can be narrowed to diet, exercise, BMI, alcohol consumption alongside biomedical factors such as timing of first birth and lactation length. The COVID response demonstrated that people can and will respond to clear leadership to change their behaviour. More recently we have seen that the habits developed in lockdowns to keep us safe are not being sustained by many. We therefore believe that to sustain change we must rely on health promotion efforts but these need to be heavily supported at a primary or community care level.

- **Behavioural: adapting screening for those with larger bodies to assist participation**. Ellie Darcy School of Population and Global Health Western Australia focussed her research on the value of collecting height and weight data at screening. They found that asking for the data did not affect screening rates but that rescreening rates decline as BMI increases and is most noticeable for second time screeners and those with a BMI greater than 35. This work continues with a focus on co designing an intervention for women with larger bodies. [38]

- **Biology**: **Later age at first birth impacts breast cancer risk**: Jessica O'Driscoll School of Public Health, Ireland looked at preliminary findings from the SPHeRE Study which is investigating reproductive factors and their association with breast density and found that the more children a woman had reduced the association with breast density (inverse relationship) while the later the age of first birth the stronger the association with breast density. This is an issue often discussed and this is the first time I have seen trial evidence. [38]

A perception precision health will cost too much alongside muted clinician ambition: We recommend that well in advance of the 10-year timeframe, we model improvements. For example, this modelling can be done for breast cancer by utilising, BCFNZ Breast Registry data. Hei Āhuru Mowai and Breast Cancer Cure, Breast Cancer Aotearoa Coalition and Sweet Louise all want to model lowering the age of screening for Māori, Pacific, Asian and those at increased risk so that we can assess benefits from reducing late-stage diagnosis for these individuals and their whānau. Will investing more in early diagnosis and more precise treatment result in savings overall and improve quality of life for individuals and their whānau?
As consumers we want clinicians alongside us with equal ambition to make such improvements. This is one example only. Once such work has been completed there also needs to be evident the courage and ambition to translate the changes into practice.

Slow registration/funding and mode of funding of new and novel treatments, tools and technologies and few trial participation opportunities: **For precision health and precision medicine to be effective we need access to new therapies and tools/assays on a timely basis and trials need to include our diverse population**. Too few New Zealanders get to participate in a clinical trial and when New Zealanders become advanced and reach the end of the road for medicines, they do not have an option to leave standard of care and pursue the latest trial options. For them it is more common that they must, with family and friends, establish a Give a Little page and hope to fund, further standard of care options more aligned with other OECD countries.

Fabrice Andre spoke at the American Association of Research meeting regarding the slow implementation of Precision Medicine. He contends that the current process of evaluating and approving treatments by cancer type is limiting the reach of precision medicine. He suggests categorizing tumours by their molecular features and potentially extending approval of a molecularly targeted therapy that is effective in one cancer type to other cancer types fuelled by the same molecular driver and above all investing in molecular testing tools to identify tumours that would respond to certain treatments. Mark J Ellis, Baylor College of Medicine, at the same meeting, spoke about the National Cancer Institutes Clinical Proteomics Technologies Initiative working on a parallel analysis of DNA, RNA and proteins of tumour samples. The need to transform trials through deep diagnosis and to prospectively gather trial groups based on that diagnosis. He also commented on the need to study molecular features at the tumour microenvironment level as relevant to identifying targeted therapies.[42]

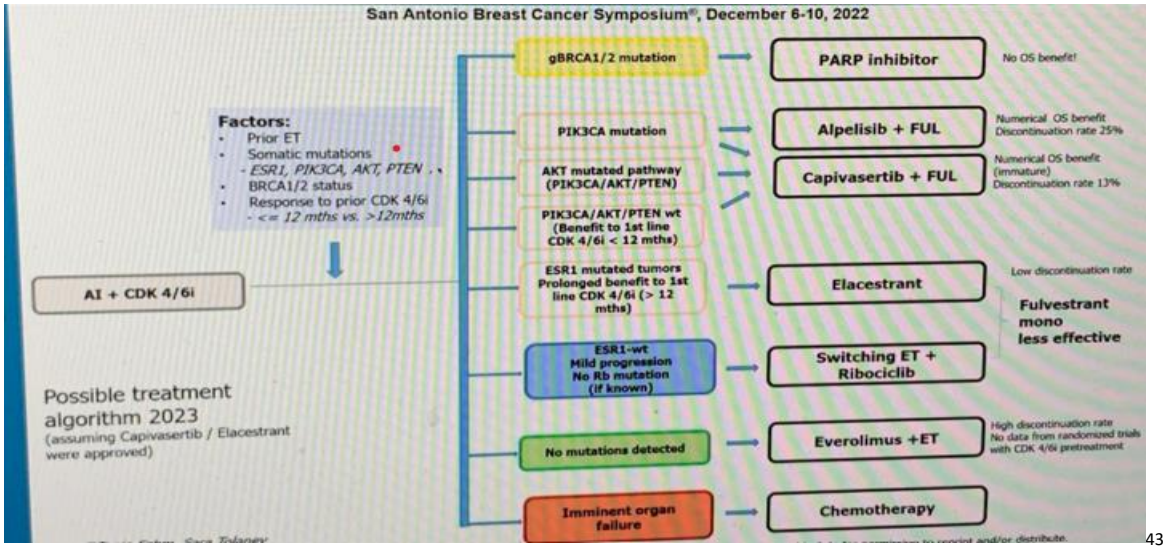
Fabrice Andre developed ASCO guidelines in 2022 regarding HR+ metastatic breast cancer patients, presented at SABCS December 2022, with helpful commentary regarding biomarker and genomic assays to guide treatment options to more precisely target therapy.

For precision medicine to work in New Zealand we need to encourage pharmaceutical companies to register and seek funding for their medicines and encourage trial options and if that is not possible to track real world data for our population. **We also need a medicines budget that can evaluate and fund precision medicines in a timely manner.**

Looking at the treatment algorithm below proposed by Fabrice Andre at SABCS, 2022 as presented by Melinda Telli, Year in Review SABCS 2022, [43] it is clear that not all medicines are suited to every patient and patients experience discontinuation. It is also obvious from this algorithm that we need access to alternative CDK4/6 inhibitors beyond Palbociclib e.g., ribociclib and or abemaciclib. You

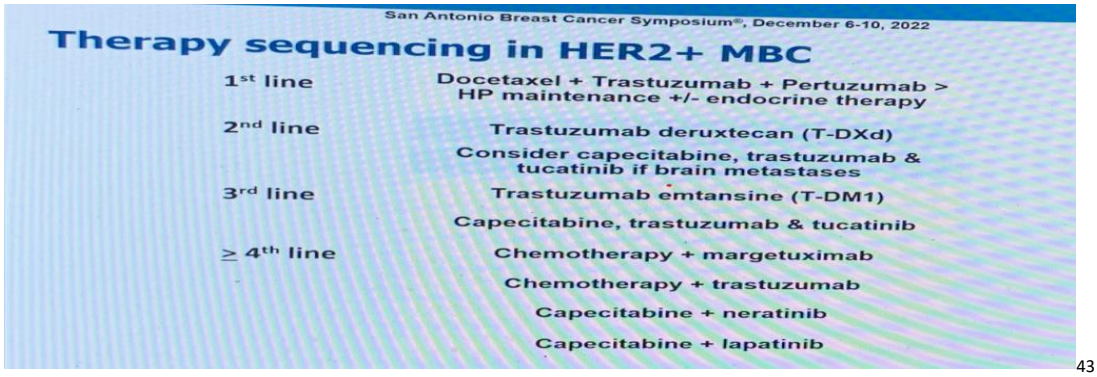
can also see that capivasertib and elacestrant may replace fulvestrant as a preferred option. It took BCAC 12 years to get fulvestrant funded, how long will it take to get these newer options funded? They are administered orally while fulvestrant requires injection by a GP or nurse practitioner. In the US they are certain the FDA will fund them in 2023. When you look at the algorithm it is clear not everyone accesses all medicines, what it shows is that we are beginning to target therapy more specifically, therefore there are more options that are identified as effective for fewer people. This is precision medicine.

Referring again to the treatment algorithm, in New Zealand there are three Medsafe-approved CDK4/6 inhibitors but just one, Palbociclib, is Pharmac funded. The mTOR inhibitor everolimus is not Medsafe approved nor Pharmac funded for breast cancer. Aleplisib is a treatment option for patients with PIK3CA-mutant tumours (in exons 9 or 20). Alpelisib and other PI3K inhibitors are not Pharmac-funded (as of September 2022), but it is Medsafe-approved (as of 18/08/2020). Capivasertib and elacestrant are expected to be FDA approved in 2023 but neither are Medsafe registered nor approved in New Zealand. [44]



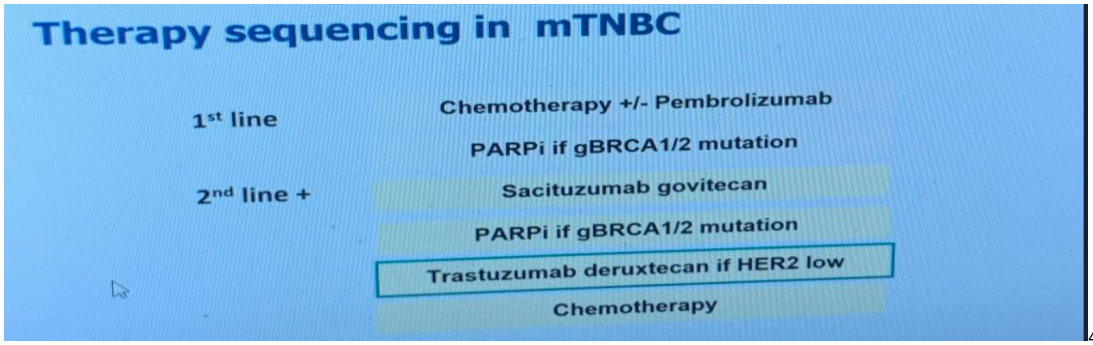
[43]

The story is similar for HER2+ breast cancer again from a presentation at SABCS , see below. In New Zealand metastatic breast cancer patients cannot access later line trastuzumab, nor trastuzumab deruxtecan (complete response for 1 in 5), tucatinib (for brain mets), neratinib or lapatinib. Pertuzumab and TDM-1 are funded for limited uses only.



[43]

Likewise, a similar picture for Triple negative metastatic breast cancer. Pembrolizomab, sacituzumab govitecan and PARPi along with trastuzumab deruxtencan are neither registered nor funded in New Zealand.



43

To summarise, New Zealand patients receive a very limited range of medicines well below the international standard of care defined in the evidence-based guidelines produced by ESMO and NCCN. **We cannot deliver precision health unless we offer precision medicine to our population.** The current situation results in a double standard of care, where patients able to fund treatments in private cancer clinics will have longer healthier lives. This creates socio-economic and ethnic inequity that is unacceptable in Aotearoa today. Any attempt to strive for precision health must include aspiration to raise the standard of care at least to the level enjoyed in other similar OECD countries. We are concerned that a precision health project led by Manatū Hauora may avoid facing this reality, given New Zealand's long-standing under-funding of medicines under the Pharmac model. **We urge the team to clearly identify access to precision medicine as a critical issue in the briefing paper**.

Picking up on the need to operate at a molecular level Francis Hunter and the Barbara Lipert carried out a project titled "The validation of Predictive Biomarkers for TDM-1 (Kadcyla)". Previously there haven't been reliable biomarkers to predict who will resist Kadcyla. Lipert and the team, following on from a Breast Cancer Research Partnership project led by Dr Francis Hunter, identified approximately 600 genes and found that TSC1 and to a lesser degree TSC2 can confer resistance either together or alone to Kadcyla. These two known suppressor genes are inhibitors and negative regulators of the mTOR pathway. CRISPR/CAS9 technology was used throughout. They also created a framework for further biomarker discovery for other trastuzumab-based drugs such as Enhertu and SYD985 used in the therapy of HER2 positive breast cancer. The data acquired through the project were used in the following grant applications: Maurice Wilkins Centre Category 2 - Lipert: 'Seeking genetic modifiers to the drug trastuzumab emtansine (T-DM1) to advance HER2-targeted therapy of breast cancer;' a successful HRC application 21/410 - Jamieson: Overcoming antibody-drug conjugate resistance in HER2-positive breast cancer' for which they have recently been awarded a 3 year $1.19M. 45

Do we have the ambition to run the trial TSC1/2 trial in New Zealand and others we hope will follow? Aleplisib following failure on TDM-1 would seem an option following a period of recovery.

- What concerns or issues do you have with precision health, or how we may adapt it in Aotearoa in the future? Areas of focus for case studies

We are concerned that prevention through health promotion will receive a stronger focus and not be coupled with an equal focus on cancer control.

We do support reducing alcohol consumption, improving diets and the need to be active however our interest would also be to address the issues highlighted in question 2 to increase prediction (cfDNA), prevention and earlier diagnosis and to better tailor treatments for patients including inhibition and gene editing alongside surgical and other biomedical options.

We wish to see increased leadership of and participation in global research as detailed in the Enhancing Aotearoa New Zealand Clinical Trials paper. [46] We want recruitment of clinical trials to ensure diversity for results to be valid for our population.

Concerned that de-escalation of treatment be accompanied by evidence-based guidelines along with more nuanced assessments including genomics and imaging.

As we move to a more precise approach it is important, we take account of all the evidence available and that we are tempered in our desire to implement without the tools needed. We want to see recurrence reduced significantly balanced by patient choice.

For example, there is strong evidence globally and locally supporting breast conserving surgery over mastectomy and we agree with this approach, when it is coupled with quality information and individual risk is assessed and patient choice is not lost. Historically breast cancer patients with multiple ipsilateral breast primaries were treated with mastectomy. However, with advances in breast cancer diagnosis, imaging, pathology assessment and management through improved staging and preoperative MRI there is now a realisation that mastectomy is not improving survival over breast conserving surgery. Some of the perceived benefits of mastectomy were not being realised. Breast conserving surgery for those who have chosen it has been associated with improved quality of life, patient satisfaction and survival benefits. It is acknowledged these are not easy decisions and shared decision making and patient choice are important. We in New Zealand have recently developed draft QPI's but these QPI's come without guidelines. International evidence indicates the trend from Mastectomy to Breast Conserving surgery is best suited to early-stage disease, where the tumour is less than 5 cm, confined to 2 breast quadrants and cN0-1, with negative margins, whole breast radiation and no BRCA mutation carriers. There is also evidence that points to significant reduction in recurrence if MRI imaging is used. (Boughey et al 2022)[58] showed the benefit of radiotherapy in association with preoperative MRI (1.7 versus 22.6 percent) recurrence at 5 years. For moderate risk genes, MRI added to annual mammography at age 40 reduced mortality by greater than 40%, MRI at 30-35 and mammography at 40 balances risks and benefits. [30] In addition, (Yadav et al, 2023)[93]presented findings from research into the risk of contralateral breast cancer which provide new information regarding risk for those with germline mutations. It is important to acknowledge that premenopausal women who carry germline mutations generally have a higher risk of contralateral breast cancer compared with women who are post-menopausal at breast cancer diagnosis. Among women with germline mutations in breast cancer predisposition genes, the study found there were no racial differences, suggesting that risk management strategies should be similar. In a further study the risk of post treatment density risk was assessed as twofold, 1 year after diagnosis and associated with a risk of contralateral breast cancer including higher stage (2-3) and

grade (3-4). [38]. These studies make clearer when mastectomy versus aggressive surveillance or preventive medication may be used."[93].

Having this level of detail will help guide decisions between patients and their care teams on appropriate screening and steps to reduce the risk of ipsilateral and contralateral breast cancer based on more precise and individualized risk estimates.

Our concern is that if we rush to deescalate without utilising the tools recommended, we will not be precise in our approach and patients will resist. Precision medicine brings with it the need to be more nuanced in our approach. Will those with multifocal breast cancer have their germline status assessed or will those with high-risk status be recommended for an MRI?

Breast conserving surgery for those who meet the guidelines and they choose it, is a less aggressive surgery, but we need to align the use of good tools with research to bring precision to the pathway.[94]

We see the need for deeper validation of tools and techniques for greater understanding for:

- non-Europeans – Māori, Pacific and Asians and others in our unique population
- For all members of our population including those under the age of 45 and those older than 65 require greater validation as these age groups were often excluded from trials

While continuing to recognise our core strengths we need to identify and implement new innovative projects including a genome 10K project for New Zealand alongside new genomic medicine projects through partnerships, investing time and resource to move us forward in Precision Health and Precision Medicine. For example:

- allocating 70% to core activities, 20% to new innovative capability and 10% to transformative capability and over time transitioning that to
- 40% core and 30% innovation and 30% transformational.

Getting the balance right will help transition us to precision health and precision medicine while raising capability and capacity.

We are concerned that precision medicine will not be given sufficient focus and that more effort will be put into prevention than control. **Precision medicine cannot be achieved without the tools identified for example genomics and imaging to help guide clinicians and patients in their decision making. In this instance we have used the example of surgery but we could replicate this discussion across the cancer pathway.**

Our final concern is whether the necessary additional funding and resource will be provided to build the capability and infrastructure to enable successful implementation.

5. Which case study areas do you think the briefing should explore? Why?

You can indicate one or more of the following (or identify any other areas of interest to you):

Genomics

Project 1 Policy Leadership for the introduction of a parliamentary bill "Preventing genomic discrimination": Government departments liaise and agree which will provide policy leadership in the development and introduction of a Preventing Genomic Discrimination bill, as a step towards legislation.

Project 2 Policy Leadership for a regulatory review and modernisation of legislation relating to gene therapy into lab-contained, biomedical applications focused more on risk than the technology involved.

Project 3 Policy Leadership for measuring and reporting breast density: we seek policy guidance to ensure that breast density be measured, reported and accepted as a risk factor alongside other risk factors as it masks mammographic breast cancer(MD) and is an independent risk factor. Mammographic Density phenotypes show 60% heritability. (Weiva Sieh et al, 2022). [38]

Project 4 Identify and implement budget, systems, processes and capability needed to enable early access to precision health and precision medicine.

Implementation of a precision health approach within Aotearoa requires high level policy and planning as well as broad input and adequate resourcing. While Te Manatū Hauora will have a leadership role in ensuring innovation and improvement are a constant driving force within our health system, it is essential that there is ongoing input from leading researchers, scientists, cutting-edge clinicians, computational specialists and technologists from both public and private sectors, health consumer representatives from patient-based NGOs, Māori, Pacific people and others, as well as industry. This inclusive approach will ensure that emerging technologies are understood and implemented early and that health innovation is fit for purpose and has social license within our population. All elements of precision health and precision medicine require infrastructure and budgetary resource to ensure the benefits are realised. A high-level overview is needed from the **Precision Health 'think tank'** described above, to provide a roadmap that takes Aotearoa's health system from where we are today to a future where precision health and innovation are accepted as standard of care. There is a need to ensure the various elements of precision health are well linked and co-ordinated. This advisory group must bring new ideas to the table, challenging the status quo and informing governments of the benefits of investing in precision health as has happened in the UK.

Project 5 Build on and continue to invest in Rakeiora through the introduction of a 10K genome project for New Zealand. The 100,000 Genomes Project developed by NHS England was instigated to improve cancer care by improving treatment and outcomes through personalised medicine. The UK works with Scotland, Wales and Northern Ireland and different scientific groups. The project decoded 100,000 human genomes to create a new genomic medicine service in the UK. It looks at a person's entire DNA, rather than specific genes or groups of genes. [47] The Genomic Medicine Service provides genome sequencing to people with certain cancers and undiagnosed rare diseases to more effectively treat disease. We suggest building on the Rakeiora project by kick starting a similar project in New Zealand. [34]

Project 6 Genomic testing at birth in line with an *e*vidence-based clinical approach in line with New Zealand's needs. NIPS over traditional screening methods for all pregnant patients with singleton

and twin gestations for foetal trisomies 21, 18, and 13. Evidence also strongly recommends NIPS be offered to patients to screen for foetal sex chromosome aneuploidy. [48]

Project 7 Develop a risk assessment tool (such as CanRisk) for New Zealand with an expectation risk will be assessed between the ages of 25-30: New Zealand to adopt the CanRisk tool. By integrating genetic data into the CanRisk Web Tool https://www.canrisk.org/) [4] along with family history, lifestyle/hormonal risk factors, common genetic susceptibility variants, and mammographic density we would further improve breast cancer risk predictions. Such a model will better inform patient decisions regarding breast cancer risk management. [14] Note: its accuracy will be dependent on the measurement and reporting of breast density. **Mammographic Density phenotypes show 60% heritability**. Weiva Sieh, Department of Population Health Science and Policy and Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY. They have shown 60% heritability while the heritability of breast cancer is 27%. They are relevant to breast cancer risk and should not be ignored. [38]

Project 8 Genomic testing introduced at the time of diagnosis for early and metastatic disease.
Genomic testing alongside digital clinicopathological data, is core to precision health and precision medicine. This could be through ctc's, ctDNA tissue and blood (we note in the US microbiome samples are also being collected) at the time of diagnosis pre and post neoadjuvant treatment to identify those at high risk, with monitoring at agreed timeframes. This will occur initially as clinical research through primary, secondary and tertiary care.

Examples from metastatic disease:

- Measuring risk through ctc's rather than relying on clinic pathological information alone for HR+ breast cancer was reported by (Bidard et al, 2022). Overall survival (OS) was better in patients when circulating tumour cell (CTC) count was used to decide between chemotherapy and endocrine therapy rather than physician choice alone. Notably, "CTC count backed the investigator's decision in most (around 60 percent) patients," Results in the 40 percent of patients with discordant treatment choices between investigators and CTC count established CTC count as a clinically relevant tool." Bidard confirmed that "Oncologists have a key role in collecting and balancing different factors when making treatment decisions for patients." Overall, the results of this study "will likely change a part of the way we understand treatment decisions" in this group of patients, Bidard said. **He believes that using CTC count could "optimize and standardize" treatment decisions for patients who have relapsed or progressed under adjuvant or first-line CDK4/6 inhibitors. Such decisions are currently very heterogeneous from one doctor, centre, or country. He also sees the need for more** integrated decision tools to help oncologists and patients navigate the different treatment options, building on biomarkers that are existing (*BRCA*, *PIK3CA*, *ESR1* mutations and CTC count) and investigational (F-18 16 alpha-fluoroestradiol-positron emission tomography, other circulating tumour DNA alterations, and genomic signatures). [49]

- Henry et al, Biomarkers for Systemic Therapy in Metastatic Breast Cancer, 2022. Candidates for a regimen with a phosphatidylinositol 3-kinase inhibitor and hormonal therapy should undergo testing for *PIK3CA* mutations using next-generation sequencing of tumour tissue or circulating tumour DNA (ctDNA) in plasma to determine eligibility for alpelisib plus fulvestrant. If no mutation is found in ctDNA, testing in tumour tissue, if available, should be used. Patients who are candidates for poly (ADP-ribose) polymerase (PARP) inhibitor therapy should undergo testing for germline *BRCA1* and *BRCA2* pathogenic or likely pathogenic mutations to determine eligibility for a PARP inhibitor. Candidates for immune checkpoint inhibitor therapy should undergo testing for expression of programmed cell death ligand-1 in

the tumour and immune cells to determine eligibility for treatment with pembrolizumab plus chemotherapy. Candidates for an immune checkpoint inhibitor should also undergo testing for deficient mismatch repair/microsatellite instability-high to determine eligibility for dostarlimab-gxly or pembrolizumab, as well as testing for tumour mutational burden. Clinicians may test for *NTRK* fusions to determine eligibility for TRK inhibitors. [50]

- Another example reported by Nicholas Turner et al, showed the benefit of ctDNA and inhibition of a pathway. 41 percent of patients had genetic alterations in the AKT pathway, 22 percent were pre/perimenopausal, 77 percent were postmenopausal, and 1 percent were male. This treatment is focused on patients whose cancer has progressed on a regimen containing an endocrine therapy. [51]

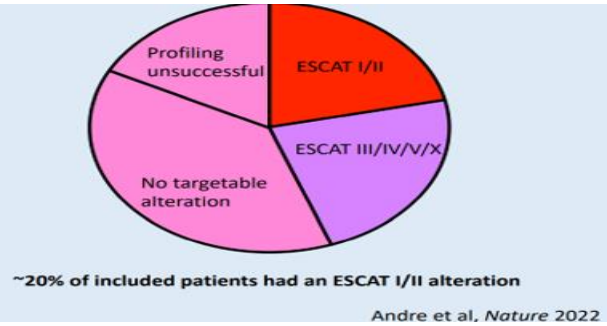
Examples from early breast cancer:

- Results from Turner et els' c-TRAK TN trial provided significant insight that treating and then testing for relapse after treatment is a waste unless tested early as 28% of patients had already relapsed. ctDNA testing needs to start for high-risk TNBC patients within 3 months. They also recommend tracking multiple mutations and focussing on a number of variants per panel. [15]
- O'Regan et al demonstrated through use of a genomic assay Breast Cancer Index (BCI) there is prognostic value in determining distant recurrence. Ovarian suppression is toxic and the benefit of the BCI was that it could detect who would benefit. The trial showed that adding ovarian function suppression (OFS) to endocrine therapy benefited a subset of premenopausal women with HR-positive, early-stage breast cancer. [52]
- Judy Boughey, M.D., of the Mayo Clinic College of Medicine and Science in Rochester, Minnesota. http://prac.co/l/2pqdxgbr demonstrated that patients undergoing lumpectomy followed by radiation therapy had acceptably low local recurrence rate of 3.2 percent at five years. However, of note patients who underwent a preoperative MRI have an even lower local recurrence rate than the patients who did not (1.7 versus 22.6 percent at five years; P = 0.002). "**The MRI finding seems important as a means of precision for patients with multiple ipsilateral breast cancer who wish to pursue breast-conserving therapy, breast MRI should be considered to evaluate for extent of disease and additional foci to aid evaluation and candidacy for breast conservation."** [53]
- Jacqueline Shaw in a presentation ahead of print at ASCO 2 June, 2022 outlined a study that demonstrated that serial postoperative ctDNA analysis had strong prognostic value in patients with early-stage breast cancer regardless of tumour subtype. Indicating that serial ctDNA may provide valuable clinical information for risk stratification of patients with breast cancer. For patients with recurrent disease, it may also open up more avenues for therapeutic interventions upon early detection of metastatic disease. On the other hand, repeated negative ctDNA tests may provide reassurance to patients. [30]
- **HER2DX** is a prognostic and predictive assay in early-stage HER2-positive breast cancer based on clinical features and the expression of 4 gene signatures (immune, proliferation, luminal differentiation and HER2 amplicon), including ERBB2 mRNA levels. In a recent study HER2DX predicted efficacy of a de-escalated, chemotherapy-free neoadjuvant regimen in HER2-positive/hormone receptor-positive breast cancer (Guarneri et al, January, 2023). [54] In a similar study but this time with a different drug HER2DX risk and immunoglobulin signature scores were significantly associated with OS from the time of diagnosis utilising the standardized HER2DX genomic assay. It was found to have potential predictive and prognostic utility in patients with advanced HER2+ MBC treated with T-DM1. [55]
- **Genomic classifier for radiotherapy**: At SABCS 2022, Per Karlsson, MD, PhD, Sahlgrenska Comprehensive Cancer Center, Gothenburg, Sweden reported that a radiotherapy trial from

the meta-analysis investigating the prognostic value of the Profile for the Omission of Local Adjuvant Radiotherapy (POLAR) in predicting the benefit of radiotherapy for patients with breast cancer was positive. It showed POLAR as the first genomic classifier to predict radiotherapy benefit, validation is ongoing but the three trials in Sweden, UK and Scotland were clear. [56]

Fabrice Andre in an ASCO guideline update in 2022 identified Biomarkers for Adjuvant Endocrine and Chemotherapy in Early-Stage Breast Cancer. They identified randomized clinical trials and prospective-retrospective studies published from January 2016 to October 2021 looking at overall survival and disease-free or recurrence-free survival to develop evidence-based recommendations. They identified 24 studies. They recommended Clinicians use: RECOMMENDATIONS:

- Oncotype DX, MammaPrint, Breast Cancer Index (BCI), and EndoPredict to guide adjuvant endocrine and chemotherapy in patients who are postmenopausal or age greater than 50 years with early-stage ER+, HER2– breast cancer that is node-negative or with 1-3 positive nodes.
- Prosigna and BCI may be used in postmenopausal patients with node-negative ER+ and HER2– breast cancer.
- In premenopausal patients, clinicians may use Oncotype in patients with node-negative ER+ and HER2– breast cancer.
- Current data suggest that premenopausal patients with 1-3 positive nodes benefit from chemotherapy regardless of genomic assay result.
- There are no data on use of genomic tests to guide adjuvant chemotherapy in patients with greater than or equal to 4 positive nodes.
- Ki67 combined with other parameters or immunohistochemistry 4 score may be used in postmenopausal patients without access to genomic tests to guide adjuvant therapy decisions.
- BCI may be offered to patients with 0-3 positive nodes who received 5 years of endocrine therapy without evidence of recurrence to guide decisions about extended endocrine therapy.
- None of the assays are recommended for treatment guidance in individuals with HER2-positive or triple-negative breast cancer.
- Treatment decisions should also consider disease stage, comorbidities, and patient preferences. Additional information is available at www.asco.org/breast-cancer-guidelines. J Clin Oncol © 2022 by American Society of Clinical Oncology. [57]



[58]

The assays referred to here are not publicly funded and have not been fully validated within our population and nor are they currently funded in Australia. They are utilised by those who can afford to pay privately. Another reason for inequity. We need to validate these assays in our population.

The MSK team at SABCS highlighted a nomogram freely available from their website www.nomograms.org which is not as accurate as other genomic assays but is free. They challenge those providing genomic assays to demonstrate predictive accuracy, calibrate against actual outcomes and discriminate so that rigorous proof can be added to clinical benefit. [59]

Project 9. Continue to research and facilitate high trial participation to better differentiate ancestral biological differences from care and social determinants to close the equity gap and to identify new biomarkers and opportunities for intervention: Examples from international studies:

Ancestry and Breast Density: To prepare for risk stratified screening it is important that research occur to better understand the implications of Single Nucleotide Polymorphism's (SNP's) for non-European New Zealanders. For example, only 39% of SNP's identified in European women are replicated in Asian women.[38] This suggests that there are significant opportunities to identify new markers of resistance.

Racial disparities – biology: Several insights in Precision Health and Precision Medicine have been discovered in other geographies. These demonstrate despite carefully treated study participants there are indications that biological factors other than disparities in care may contribute to inferior outcomes in racial minorities and that we all differ including at a microenvironment level. (Yara Abdoe, SABCS 2022). [60]

The Rx Ponder trial: For example the recurrence scores based on the 21-gene breast-cancer assay have been clinically useful in predicting a chemotherapy benefit in hormone-receptor–positive, (HER2) negative, axillary lymph-node–negative breast cancer. In women with positive lymph-node disease, the role of the recurrence score with respect to predicting a benefit of adjuvant chemotherapy is unclear. It has been indicated that Black women with HR+/HER2- BC, 1-3 involved LNs and RS ≤ 25 have worse outcomes compared to White women despite similar RS results. This is particularly so in the first 5 years but diminishes in time with black women experiencing higher recurrence up to 5 years. There remains an important need for novel approaches to improve clinical outcomes particularly for non-European women. It is suggested that tumour biology (such as proliferation gene groups) may differ by race, contributing to noted disparities but there was also caution that this continue to be teased out particularly social determinants including access to care. Future analyses of gene groups by race in RxPONDER will be explored. For this trial concern remains regarding Outcome differences may also be due to health care access issues. Future analysis of Social Determinants of Health (SDOH) based on geographic location will also be explored along with the likelihood of treatment completion and adherence by race and ethnicity beyond the first year.

These results indicate that for non-European New Zealanders we also need to complete this work if we are to utilise such tools. See the US results below.

Table 1. IDFS by Race and Ethnicity

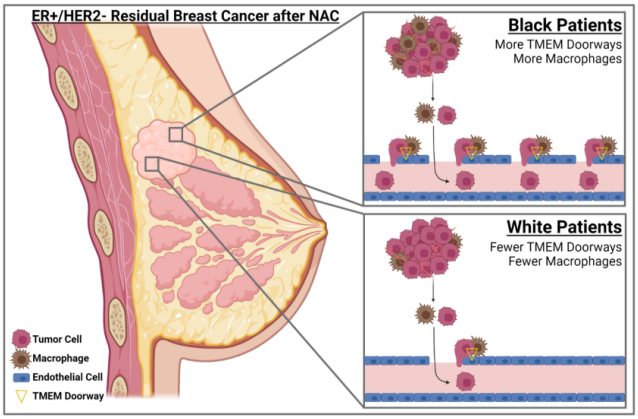
Table 1. IDFS by Race and Ethnicity

Race/ethnicity	N	IDFS Events	5-year IDFS, %	Adjusted HR (95% CI)
NH Whites	2,833	353	91.5%	1.00 (referent)
Asians	324	27	93.9%	0.65 (0.44-0.97)
Hispanics	610	72	91.4%	0.91 (0.70-1.17)
NH Blacks	248	42	87.0%	1.38 (1.00-1.90)

[60]

Tumour Microenvironment: There are also indications of important differences as shown in Burcu Karadal Ferrina et al, Einstein College of Medicine, New York's findings presented at SABCS 2022. This team found a disparity in the tumour microenvironment and outcomes in residual breast cancer treated with neoadjuvant therapy as outlined in the graphic below. The highlight that a high tumour

microenvironment score is an independent risk factor of inferior survival following NAC and will require closer surveillance. They suggest that racial disparity in outcome may be due to a more pronounced pro-metastatic tumour microenvironment (increased TMEM doorway density) in black patients with residual ER+ breast cancer. On the other hand, no differences were seen in stem cells. See graphic below.



1. High-TMEM doorway score is an independent prognostic risk factor of inferior survival in patients with residual cancer after NAC.

2. Racial disparity in outcome may be due to a more pronounced pro-metastatic tumor microenvironment (increased TMEM doorway density) in Black, compared to White, patients with residual ER+/HER2- breast cancer.

3. Prognostic factors:
- **Tumor size – (established)**
- **Lymph node status (local spread - established)**
- **TMEM doorway score (distant spread - proposed)**

61

As stressed throughout this paper to gain precision oncology benefits for New Zealanders we must better understand our population and investigate whether social determinants of health including access to care and treatments are causing these disparities or biological differences not yet understood.

b. Pharmacogenomics to Multi-omics and Infrastructure

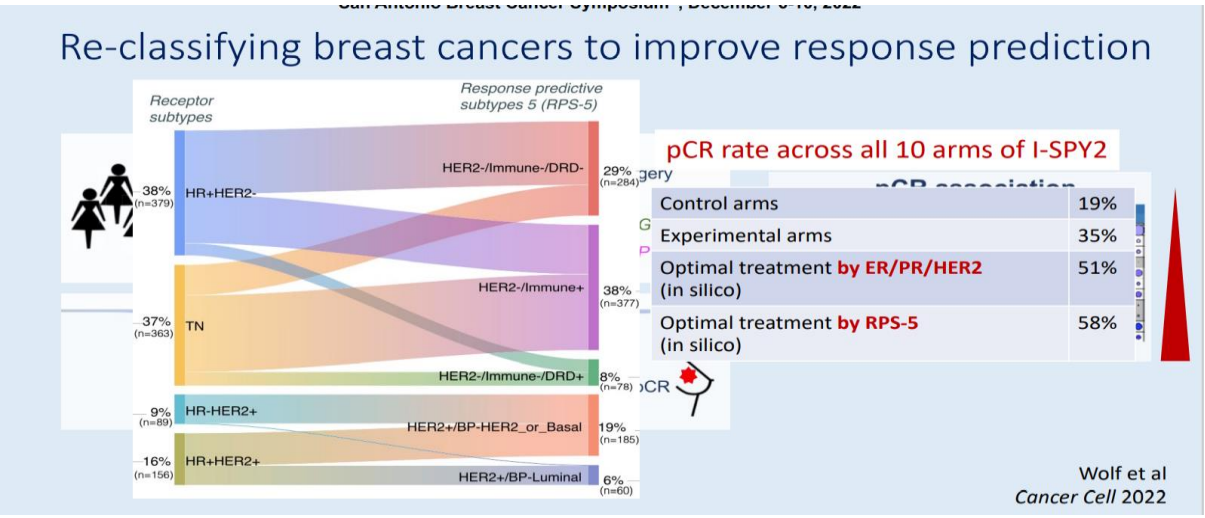
As noted at San Antonio in December 2022 by far the majority of research and trial updates now include genomic information in their analysis allied with specific therapeutic responses offering improved outcomes.

For example: Lisa Carey et al, presented at SABCS and published in January 2023 that there is prognostic and predictive value in combining immune-related gene expression signatures vs tumour-infiltrating lymphocytes in early-stage ERBB2/HER2 Positive Breast Cancer. They found by looking at two trials that when both TILs and gene expression are available, the prognostic value of immune-related signatures is superior. 62

Likewise, the Aurora Project utilised RNA sequencing, tumour/germline DNA exome and low-pass whole-genome sequencing and global DNA methylation microarrays to find that expression subtype changes occurred in ~30% of samples and were coincident with DNA clonality shifts, especially involving HER2. They stress that if medically possible it is desirable to biopsy and characterise metastatic disease as it has likely changed relative to the primary tumour. HLA-A methylation showed worse survival outcome, even when adjusting for stage and subtype. These findings have implications for treating individuals with metastatic breast cancer with immune and HER2- targeting therapies. In performing multiplatform analyses of primary tumours and metastases, epigenetic,

genomic and transcriptomic evolution could be explained including a molecular explanation of loss of immune cell features impacting therapy. i.e., Immune Checkpoint inhibitors (ICI's) as they have little impact on HLA-A low tumours as they cannot be recognised by CD8+ T cells but could be targeted by DNA methylated drugs in combination with ICI's (45). Microenvironment differences varied according to tumour subtype; the ER+ /luminal subtype had lower fibroblast and endothelial content, while triple-negative breast cancer/ basal metastases showed a decrease in B and T cells. In 17% of metastases, DNA hypermethylation and/or focal deletions were identified near HLA-A and were associated with reduced expression and lower immune cell infiltrates, especially in brain and liver metastases. [63]

In New Zealand in the public system this form of refined analysis does not occur. Relying on earlier analyses of subtype is not even reliable as there is growing fluidity or cross talk with subtypes as seen in the graphic below from Wolf et al, 2022. Wolf et al. use gene expression, protein levels, and response data from 10 drug arms of the I-SPY2 neoadjuvant trial to create new breast cancer subtypes that incorporate tumour biology beyond clinical hormone receptor (HR) and HER2 status. Use of these response-predictive subtypes to guide treatment prioritization is another step towards precision medicine.[64]



In further news relating to pharmacogenomics , GPs in England are to start genetic testing of patients before prescribing statins, antidepressants and PPIs in the first-ever NHS pilot of routine genetic testing to guide drug choice in primary care which will begin in early 2023 in north-west England, with plans for it to become a national programme if successful. (Wilkinson et al, October 2022). [65]

Therefore, we are very interested in pharmacogenomics but we raise the question how deep the analysis needs to be, to be worthwhile.

With recent advances in diverse high-throughput omics technologies (e.g., next-generation sequencing or mass spectrometry), there is a growing interest in taking advantage of such technologies. Scientists have started to integrate these complementary technologies, to investigate the roles and actions of different complete sets of molecules (e.g., genomics, proteomics, transcriptomics, epigenetics, multi-omics etc.), as well as various posttranslational modifications (e.g., methylation, phosphorylation, glycosylation, etc.) in pharmacology.

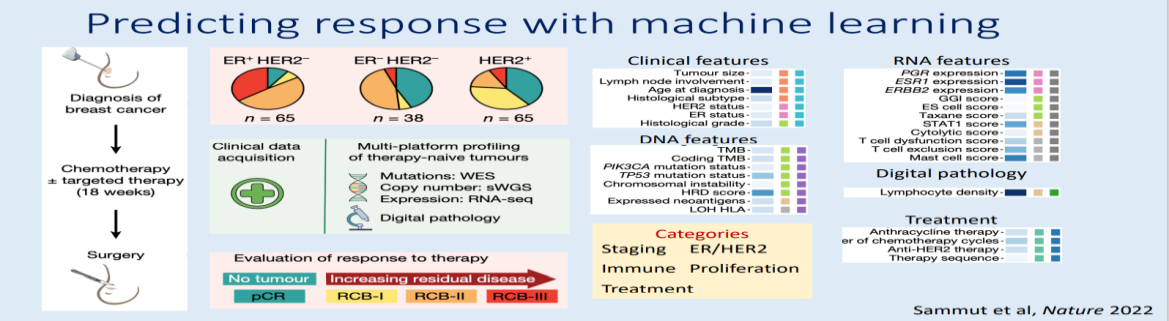
For immunotherapy prognostic assays to have true utility they need to be a marked improvement over the status quo, which includes using PD-L1, MMR, MSI, and TMB to predict if a patient will respond to immunotherapy.

Is using transcriptomics, proteomics, multi-omics different from using tests that have been used in the clinic for years? We can only imagine that with significant investment happening in the multi-omics field now and over the next 10 years there will be significant advancement and so we suggest for our population we need to look at this now as well as into the future because as we have seen with genomic assays and risk stratification tools, that if these multi-omic assays are not validated on our population (through trials and research) we will again have equity concerns.

Research in this area can be used to conduct studies revealing disease pathways and facilitating biomarker discovery and drug development comprehensively. These broader analyses promise new and better treatment strategies and paradigms for patients in the coming years.

The future of oncology will involve treatment response assays. With care these may provide some of the answers which have not been forthcoming to date. RNA-seq. allows detection of qualitative and quantitative changes in RNA expression across the genome in clinical samples and is increasingly being used as an adjunct to diagnostic exome sequencing and whole-genome sequencing. (Shamika Ketkar, Jama Oncology 2022)[66]

Sammut et al, Nature 2022 shows clearly how machine learning may augment such analyses.



[67]

We need to do such work for our population and in this instance while recognising it will take time.

In the meantime, accurate predictions of drug responses require the use of models that accurately reflect tumour complexity and heterogeneity. Patient-derived explants (PDE) allow the direct evaluation of drug responses on individual patient tumours without manipulation of the tissue material. Freshly resected tumour pieces (approx. 1mm) are cultured directly following surgery on gelatine sponges where they remain viable for up to 21 days. Since they do not require enzymatic digestion, they retain native tissue architecture, and have an intact tumour microenvironment, including immune cell infiltration.

Project 10. Develop PDEs as a clinically relevant model to investigate patient-specific drug responses.

Emma Nolan AMRF Douglas Goodfellow Repatriation Fellow at the University of Auckland has a breast cancer research group in the Centre for Cancer Research. Her group are generating a collection of patient-derived 3D tumour organoids from New Zealand women diagnosed with breast cancer. These organoids will be used as a tool to study the molecular mechanisms driving cancer progression, with a particular focus on tumour-stromal crosstalk. In addition, Breast Cancer Cure will fund Emma from Mar 2023, for the development of patient derived explants. Accurate

preclinical models that can better predict individual patient responses to therapies are urgently needed to improve treatment outcomes for breast cancer patients.

Patient-derived explants, retain key features of the donor tumour including spatial organisation and immune cell infiltration. Recent studies in other cancer types have demonstrated their exciting potential for rapidly and robustly evaluating drug efficacy, including for immunotherapies.

Using freshly resected tumour tissue from NZ women with breast cancer, this study will develop and optimize a population-relevant tumour explant platform **for the rapid evaluation of breast tumour responses to therapy**. The collection of tumour tissue is ethically approved for two Auckland Hospitals to examine anti-tumour immune responses within explants and determine whether these can be modulated using immunotherapy.

The successful development of a low-cost, rapid platform for therapy selection and patient stratification has significant potential for improving patient outcomes and avoiding unnecessary treatments. Ultimately, these models could support the implementation of personalised medicine for breast cancer patients in Aotearoa New Zealand. To do so they need to be taken into the genomic and proteomic and transcriptome space.

Importantly, recent studies using glioblastoma and gastric cancer PDEs have demonstrated intact anti-tumour immune responses that could be modulated using immunotherapy. [68,69.]

In breast cancer, PDEs derived from ER+ patients have been shown to retain oestrogen responsiveness [70], while cytokine stimulation of explants from non-cancerous breast tissue can trigger macrophage activation and polarisation, demonstrating a functional immune response. [71] Emma has also previously generated a modified (sponge-free) explant model from pre-malignant *BRCA1*-mutated breast tissue, showing they are amenable to *ex vivo* drug treatment. [72]

The team are recruiting a population-relevant cohort of women for these collections, aiming to achieve similar representation of NZ European, Māori and Pasifika women in the patient cohort.

For this study, they will use these same tissue collections to establish PDE cultures in parallel to organoid generation, to validate them as alternative preclinical breast cancer models. The implications of different ancestry and SNP's is relevant for non-European New Zealanders to prepare for risk stratified screening models using SNP's. Research is needed. Explant optimisation will be supported by collaborator Dr Claire Henry (University of Otago, Wellington), who is currently developing PDE cultures for endometrial cancer.

Spatial transcriptomics is also a follow-on aspect of this work through Dr Saem Park (University of Auckland) to examine pathways activated/suppressed in response to immunotherapy.

This work is being done with a high level of awareness of ethnic disparity in breast cancer prevalence and survival within NZ, with Māori and Pasifika women experiencing alarmingly worse outcomes [2, 81]. This indicates the urgent need to reduce disparities in breast cancer outcomes for Māori and Pasifika women, and the importance of studying this disease in models that are relevant to our unique population. This is an important step towards avoiding further inequalities – as any new biomarkers, treatment strategies or biological mechanisms that are identified through this research (or future studies utilising these models) will be immediately relevant to Aotearoa NZ patients. This is critical for preventing inequities in accessing or benefiting from research outcomes. In addition, this research will serve as a platform for future discovery that could ultimately contribute to the

development of better therapies to treat breast cancer and thus improve survival rates for Māori and Pacific women.

Emma's BCC funded study will serve as a proof of principle that breast tumour explants are a clinically relevant model for the timely assessment of drug efficacy. This will provide evidence to support the use of explant models for personalised medicine in NZ and will provide a foundation for future studies to correlate drug response *ex vivo* with patient outcomes. Importantly, explant culture is inexpensive, does not require manipulation of tissue material, is achievable within a short-time frame and without the need for specialized equipment. These features make it a highly attractive strategy for precision medicine. Through this research, the team will assess the feasibility of using PDEs to inform clinical decisions in the future.

Project 11. Partner and collaborate locally or globally for analysis of tumours and the tumour microenvironment to determine biomarkers genomically targeted medicine for our population.

Emma sits within The Centre for Cancer Research, University of Auckland Te Aka Mātauranga Matepukupuku (Te Aka), the largest cancer research centre in the country in terms of the number of researchers involved. It seeks to collaborate with patients and clinicians and deepen relationships with Te Aka Whai Ora and Te Whatu Ora as well as with clinical, philanthropic, community and industry organisations. In the short term, the centre is working with Te Aho o Te Kahu on building national cancer data sharing infrastructure [34]. That project will bring together about 40 researchers who work on large data sets.
Longer term, they seek to work directly with clinicians, cancer patients and patients' whānau and aim to improve cancer care, treatment and prevention for individuals, whānau and communities across Aotearoa New Zealand, now and into the future. [82]

Collaborate for metagenomics.

As breast cancer patients going through treatment we are required should our temperatures spike to go to hospital to be treated for a suspected bacterial infection. We understand that the process when we enter hospital is to "save our lives" through dosing of significant broad-spectrum antibiotics. We query, "how will our bodies cope with this additional onslaught". The following process described by Eric Topal provides an alternative in the name of metagenomics.

When presenting with possible sepsis multiple blood cultures are drawn and there is then a wait for a few days for results indicating a pathogen and a list of antibiotics that may be useful. The patient is bombarded with "empiric, broad spectrum antibiotics" to cover all the bacteria that are thought to be potentially causal, with implicit acknowledgement that viruses and other pathogens (fungi, parasites) won't be covered by the antibiotic cocktail. He asserts this cocktail may not even target the underlying pathogen and has the potential to be toxic for kidneys and other vital organs and is typically continued until the cultures come back. Often the cultures are negative, not revealing a/the pathogen, or show a contaminant, so, dependent on the patient's clinical condition, the cocktail is continued for several days or longer.

In contrast, "clinical metagenomics" takes an agnostic approach as to what is the causative pathogen. As shown in this excellent review, sequencing can be performed on anybody fluid or tissue and there are several steps required, besides the sequencing, that include library preparation and bioinformatic analysis. There is no assumption. The sequence tells the story in place of a clinician's intuition for what might be the cause of infection.

Genome sequencing provided a critical navigational guide for the SARS-CoV-2 pandemic, to design vaccines and then to provide surveillance of the evolution of the virus over time across the world.

Some of us thought metagenomics would become routine but as Topal asserts there has been an unwillingness by health systems to invest in getting this technology integrated to patient care.

Is it due to a lack of funding? For this to be a reality teams need to invest in desktop sequencers, reagents, training, dedicated teams, and bioinformatic support. What is *best way to care for patients?* The rise of "pocket sequencers" should raise capability and lower costs. Investment in interpretative tools would be wise, for greater diagnostic accuracy. UCSF, recently published the integrated use of metagenomics of the pathogen with host gene expression in critically ill patients, which identified 99% of confirmed sepsis cases, and the ability to separate out sepsis from non-sepsis etiologies. There has already been a published series of 34 patients in the intensive care unit in London where clinical metagenomics of the sputum *within 8 hours* led to the correct diagnosis with 92% sensitivity and 82% specificity, identifying unsuspected pathogens (such as Aspergillosis) and the anticipation of antibiotic resistance for bacterial infections. That workflow of 8 hours was also shown to be possible for whole genome sequencing of critically ill patients at Stanford University—not for infections but for undiagnosed illness via the host genome, a highly complex task.

As consumers we want this on the list of issues to be discussed. [83]

An example from the UK of partnership and collaboration: UK Initiative to transform outcomes for cancer patients based on the genomic medicine focussed on immunotherapies and vaccines.

Secretary of State for Health and Social Care Steve Barclay signed a memorandum of understanding with BioNTech SE to bring innovative vaccine research to England with the potential to transform outcomes for cancer patients. It aims to deliver 10,000 personalised therapies to UK patients by 2030 through a new research and development hub. It will help accelerate clinical trials of personalised immunotherapies for cancer and infectious disease vaccines. Cancer patients will get early access to trials exploring personalised mRNA therapies, like cancer vaccines. It is recognised that no two cancers are the same and mRNA vaccines will contain a genetic blueprint to stimulate the immune system to attack cancer cells.

Access to the trials will be through the Cancer Vaccine Launch Pad, being developed by NHS England and Genomics England. It will help to rapidly identify large numbers of cancer patients eligible for trials and explore potential immunotherapies and vaccines across multiple types of cancer and infectious diseases. The collaboration will cover various cancer types and infectious diseases affecting collectively hundreds of millions of people worldwide. Trials for innovative treatments could start as early as autumn 2023. It aims to help patients with early- and late-stage cancers. If successfully developed, the cancer vaccines could become part of standard care. Steve Barclay highlighted a focus on breast, lung and pancreatic cancer to provide targeted, personalised and precision treatments using transformative new therapies to both treat the existing cancer and help stop it returning.

This agreement builds on this government's promise to increase research and development spending to £20 billion per year. The launch pad will complement the ongoing work of the NHS Genomic Medicine Service built on the 100K genomic project, which helps patients access the latest testing technologies and ensures they are given more targeted precision treatments for their cancer, with transformative approaches and better outcomes.

BioNTech's investment will include setting up a new research and development hub and offices in the UK. Drug development will be accelerated without cutting corners through collaboration by accelerating the development of immunotherapies and vaccines.

If successful, this collaboration has the potential to improve outcomes for patients and provide early access to cancer immunotherapies as well as to innovative vaccines against infectious diseases – in the UK and worldwide. National Clinical Director for Cancer at National Health England (NHSE), Professor Peter Johnson focussed on a drive toward efforts to diagnose cancers at the earliest possible stage and providing an opportunity to improve treatments. The team believe that mRNA technology has the potential to be a transformative approach in a number of illnesses, and seek to find out how to vaccinate people against their own cancers to improve people's chance of staying cancer-free. [84]

We should refrain from thinking we cannot achieve something similar but different here. We have recognised institutions including the Malaghan Institute and others. We as consumers want such aspiration to be within our future but doing it our way.

Project 12: Collaborate for genomically targeted immunotherapies and CAR-T therapies.

Last August, Carvykti – a treatment in which a patient's cells are taken and modified to create cancer-killing Car-T cells, before being reinserted to become living drugs – became the second-ever GMO to be approved for uncontrolled release in New Zealand. [18]

We are building capability in gene therapy as already mentioned where Hilary Longley, an Auckland researcher who led the world-first trial, targeting hereditary angioedema (HAE), now sees exciting potential for the cutting-edge tech to be turned against a raft of other genetic disorders.

We in New Zealand need a regulatory review focused on such lab-contained, biomedical applications focused more on risk than the technology involved.

The therapy was provided at the New Zealand Clinical Research facility in Auckland, with minimal side effects. After a single treatment, the participants either had no more attacks of swelling or a dramatic reduction and then cessation of attacks after a few weeks. "It looks as if the single-dose treatment will provide a permanent cure for my hereditary angioedema patients' very disabling symptoms." Fourteen months later, all have been able to stop their HAE medicine, each costing more than $1500.

Since the New Zealand trial, family members of participants and patients in the Netherlands and the UK have received the same treatment. Having recently presented the early results, Longhurst was now preparing a randomised, double-blinded, placebo-controlled trial. More widely, she saw "huge potential" for development of similar CRISPR-Cas9 treatments for other genetic disorders. "I think we're at the dawn of a new age of treatments where, if we can pinpoint the gene, we might be able to sort out the problem in a single treatment ... it's really exciting to be a part of."

CRISPR-Cas9 has been explored in diseases ranging from cystic fibrosis to hemophilia, with promise for more complex illnesses like cancer, heart disease and HIV.

It is important we identify therapies with optimal efficacy for patients prior to treatment, or identifying drugs that patients are unlikely to respond too.

In other news a man with bile duct cancer and high mutation burden was given a year to live and provided an immunotherapy drug that is in use for lung, kidney and oesophageal cancer. It helps the immune system recognise and attack cancer cells. The treatment, given by a drip helps a person's own immune system fight cancer, when combined with standard chemotherapy. The Guardian Fri 30 dec 2022. [85]

In contrast Invitae, a global genomics testing company, along with others provide pharmacogenomic PGx testing ordered *proactively* before medications are prescribed for a medication known to have evidence-based, actionable clinical guidance from the Clinical Pharmacogenomics Implementation Consortium (CPIC®) and/or United States Food & Drug Administration (FDA). Once again, these tests well suited to European New Zealanders will not have been validated on our more diverse and unique population.

Similar, to reviewing renal and hepatic function before prescribing a medication, or MRI screening, pharmacogenomic (PGx) results are another key variable to consider before prescribing a medication. The implementation of pharmacogenomic testing with YouScript®* has been shown to decrease emergency visits, readmissions, hospitalizations and costs in multiple peer-reviewed studies.

Invitae's 38-gene testing panel analyzes a patient's genes and the potential metabolic impact on certain medications,[8] covering 98%** of high-evidence drug-gene interactions listed by the Clinical Pharmacogenetics Implementation Consortium (CPIC) as A or B or as actionable, recommended or required by the FDA. Invitae also offers a 15-gene testing panel specific to mental health, which covers 73%** of medications with high-evidence drug-gene interactions as listed by the Clinical Pharmacogenetics Implementation Consortium (CPIC) as A or B or as actionable, recommended or required by the FDA. This includes 100% of the mental health medications with high evidence of drug-gene impact. ***Excludes genes that as of 4/2022 are associated with particular genetic diseases, independent of any impact gene variants might have on drug selection/dosing.*[86]

Invitae regularly report strategic partnerships, for example most recently with Worldwide Clinical Trials.

Project 13: Develop multi-omics ability.

Multi-omic classifiers were an emerging theme at San Antonio Breast Cancer meeting in December 2022.

- **Proteogenomic analysis** of triple-negative breast tumours revealed a complex landscape of chemotherapy response associations, including a 19q13.31–33 somatic deletion encoding genes serving lagging-strand DNA synthesis (LIG1, POLD1, and XRCC1), that correlate with lack of pathologic response, carboplatin-selective resistance, and, in pan-cancer studies, poor prognosis and CIN. [87]
- **Quantitative radiomic features** were extracted from contrast-enhanced MRI to construct a breast cancer radiomic dataset (n = 860) and a TNBC radiogenomic dataset (n = 202). Radiomic signatures were developed and validated to fairly differentiate TNBC from other breast cancer subtypes and distinguish molecular subtypes within TNBC. A radiomic feature that captures peritumoral heterogeneity is determined to be a prognostic factor for recurrence-free survival (p = 0.01) and overall survival (p = 0.004) in TNBC. Combined with the established matching TNBC transcriptomic and metabolomic data, the team demonstrated that peritumoral heterogeneity is associated with immune suppression and upregulated fatty acid synthesis in tumour samples. This multi-omic dataset serves as a

useful resource to promote precise subtyping of TNBC and to understand the biological significance of radiomics. [88]

- **The tumour microenvironment** (TME) was systematically mapped in this study into TME structures in situ using imaging mass cytometry and multitiered spatial analysis of 693 breast tumours linked to genomic and clinical data. Ten recurrent TME structures that varied by vascular content, stromal quiescence versus activation, and leukocyte composition were identified. These TME structures had distinct enrichment patterns among breast cancer subtypes, and some were associated with genomic profiles indicative of immune escape. Regulatory and dysfunctional T cells co-occurred in large 'suppressed expansion' structures. These structures were characterized by high cellular diversity, proliferating cells and enrichment for *BRCA1* and *CASP8* mutations and predicted poor outcome in estrogen-receptor-positive disease. Spatial organization linked to local TME function and could improve patient stratification. [89]

AI models will in the future will augment or enhance precision medicine.

October 17, 2022, The Graduate Center, CUNY made known their research team has created an artificial intelligence model that could significantly improve the accuracy and reduce the time and cost of the drug development process. The new model, called CODE-AE, can screen novel drug compounds to accurately predict efficacy in humans. [90]

One big reason we haven't seen clinical metagenomics increase in use is *our culture*, there's considerable resistance to change in medicine, despite the alluring aspects of this technology.

This can be done, but there appears to be no drive or incentive to change or adopt this technology for routine medical practice.

Computational Pathology (CPATH)

Project 14: Computational pathology including AI and Machine learning. An example we wish to highlight is a project led by Gavin Harris Anatomical Pathologist, Kairangahau mate tinana, Anatomical Pathology, Canterbury Health Laboratories, Waitaha, Canterbury. This project began in 2019 with funding from the Breast Cancer Research in New Zealand Partnership (HRC, Breast Cancer Cure and BCFNZ) [91]. In 2021 it was funded by a HRC Health Delivery Research Activation Grant (Computer Assisted Diagnosis in Pathology: Guiding a pathway to translation HRC # 21/1018), and more recently funding was agreed by Te Tītoki Mataora Stage 2 Research Acceleration Programme and Breast Cancer Cure from February 2023-24.

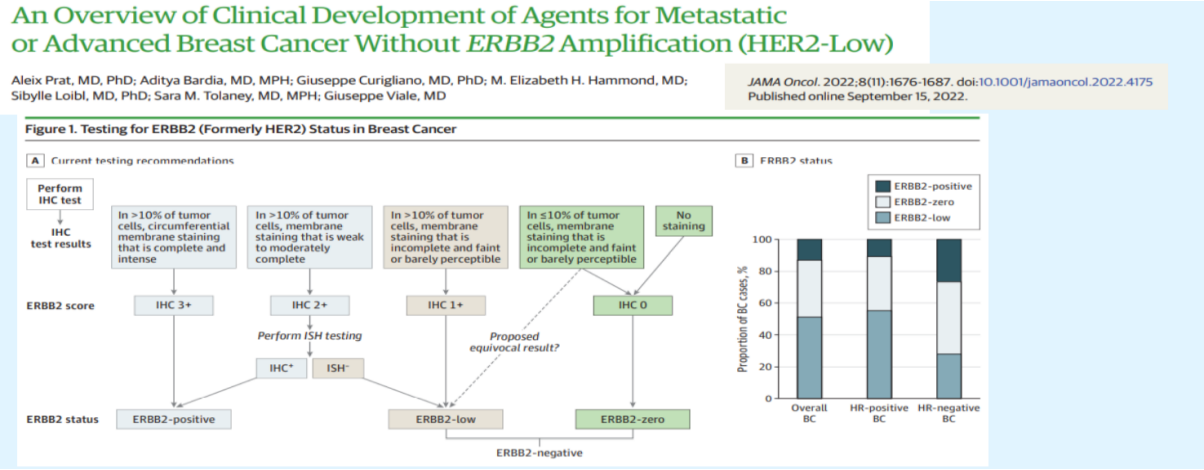
- To develop computational algorithms that can be applied to pathological samples of breast cancer to provide novel approaches to diagnosis and assessment
- To undertake multistakeholder engagement in computational approaches to breast cancer pathological assessment for the New Zealand context
- To develop computational pathology algorithms which align with an ethical framework informed by 2, that seeks to improve health equity and fairness.

Successful implementation will assist and facilitate speed of patient clinician decision making. It will improve productivity in pathology and provide fast access to detailed diagnostic results. Ultimately it will provide more detailed clinical information within the public system from genomic to validated biomarker data. We would like to see this project gain recognition as a vital aspect of New Zealand's

Precision Health and Precision Medicine infrastructure. For example, core elements of clinical assays which have been in use globally for several years OncotypeDX, Mammaprint, PAM50, Prosigna etc could be brought within this model.

- Communities are being consulted regarding this change and the ethical framework required for its success.

Breast Cancer nomenclature or biomarker classification is changing and CPATH will be required to bring the level of granularity not possible through current IHC assays. The following slide was shared by David Rimm, Pathologist, Yale, SABCS 2022 in the session titled Defining HER2 Low: A pathologist's perspective, regarding the recently identified subtype HER2low as an example where greater computational granularity is required. [92] Other speakers in the same session including Dr Siziopikou confirmed she saw concordance for HER2 low across studies as acceptable at 80% but acknowledged that as subtypes changes are dynamic over time, any HER2 low being recorded at any time, would be relevant. She added that novel assays may help if data is validated in larger trials. David Rimm's comment was that it is important that assays have the correct linear range rather than limit of saturation and he saw the need for HER2 readings in attomoles (amol) per square millimeter.



Radiology AI

Project 15: AI in Breast Screening

We need to improve earlier diagnosis to reduce the risk of advanced cancers to improve mortality. Multifactorial risks like 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. **Reference:** 7th Biennial Conference, Why Study mammographic Density, 27-28 September 2022 – in person and online. [38]

- Our Breast Screen system was established with the best evidence available at the time. It is for those at average risk (not defined) and its success depends on GP or self-initiated uptake and ongoing participation. The objective is to reduce mortality.
- We have seen a reduction in mortality over several years but these rewards cannot be solely attributed to the screening pathway and these outcomes are not evenly shared within our population.

Recent randomised and observational trial outcomes and research globally have reinforced the opportunity to optimise population-based screening programmes through risk stratification using new technologies and Artificial Intelligence (AI). A focus on earlier diagnosis particularly for Māori, Pacific, Chinese and others at high risk in line with precision health is important. Screening programmes today are suboptimal for those diagnosed symptomatically while those who do not develop cancer perceive little benefit from a one size fits all screening programme over their lifetime. One way to optimise our screening programme putting aside access, coverage, participation, frequency and age extension.

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. " Artificial intelligence imaging in medical imaging – what radiologists need to know. Goergen, Frazer, Reddy , 03 March 2022. **https://doi.org/10.1111/1754-9485.13379.** [38]

Reduction in false positives and workload: Mads Neilson Professor Image Analysis, Computational Modelling and Geometry, University Copenhagen, Denmark. (1) Rolled out an AI programme in Denmark which 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 not being able to screen everyone within the required interval, a shortage of radiologists and concerns regarding quality and cost. It helps them to identify mammograms in less urgent need of a double reading and reduced recall rates by 17%. [38]

Average risk women at substantial risk of breast cancer: John Hopper, Australian genetic epidemiologist and professor at the University of Melbourne, Australia (1) 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 and considerable care in implementation. [38]

Prevention and Risk Stratification within screening interval: Michael Eriksson, Department of Medical Epidemiology and Biostatistics , Karolinska Institutet Sweden. (1) Their AI programme KARMA provides information on long term performance of an image based short term risk model for breast cancer. They see a role for prevention (lifestyle, prophylactic medication), ability to assess risk across 10 years, reduction of late stage and higher-grade diagnoses along with personalised screening. Short term risk identifies women who 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. He said 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. They have developed three AI models. Model

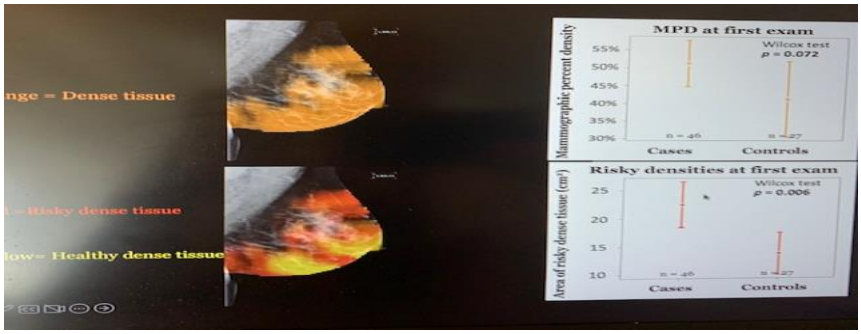
1 is based on age and image features only; Model 2 is based on family history and lifestyle factors and Model 3 adds genetic determinants. For this study they utilised Model 1. They validated against Tyrer- Cuzick. The KARMA risk model outperformed Tyrer-Cuzick for a 10-year view. The AUC's for KARMA ranged from 0.76 to 0.66 over 1-10 years. While Tyrer-Cuzick ranged from 0.67-0.62. It is a model that is clinically useful in identifying women who will benefit from intervention. This model is not technology dependent. [38]

Determining Future Risk, Stratification and modality selection: Per Hall, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Sweden (1). Individualised prevention and screening of breast cancer: the KARMA experience. The purpose of a mammogram is to detect cancer but there is information in a mammogram which can determine the future risk of breast cancer: parity, age at first birth, breast feeding, density, use of HRT. These features are intuitive to radiologists. AI helps you know whether you need a second reader, for those at risk it also helps to identify false negatives. They recommend using Tomosynthesis for breast AI models i.e., 2-300 images and not 4 and use 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%) at risk with differing risk ratios from 1 for low to 25 for very high. They can predetermine interval cancers 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 preventative measures. They recommend that arbitrary cut offs for risk models are not helpful and it is better to assess risk over the interval screening period. They see the next step as modelling longitudinal information which is what radiologists do. This information suggests that stratifying our population as at average risk and high risk is inadequate based on these findings. Does it also mean we need to boost our symptomatic pathways and better stratify risk as they stress it should not be arbitrary. [38]

Prediction of interval cancers and invasive cancers: Celeste Damiani, Queen Mary Hospital London (1) adoption and implementation of the MIT model (MIRAI) in a medical facility in London. This model is technology dependent (HOLOGIC). It does include density. MIRAI 3-year risk was associated with future interval and screen detected cancers. Stronger predictor of interval than screen detected. Slightly more predictive for invasive than in situ. Seen as a predictor of 3–6-year risk, accuracy high 0.70 for HR+ breast cancers. [38]

There is no doubt that Sweden is successfully using mammography and tomosynthesis driven AI to assess risk and find cancers earlier and with more precision. Their interval cancer rate which I cannot now find was low.

Healthy and Risky dense tissue indicated by brightness on images is meaningful: Andre Kahlil the University of Maine (1) looked at the differences between healthy and risky dense tissue utilising spectrum technology as shown below, red being risky and yellow healthy – these are the brighter markings seen on MRI. Visually this tells you we are not all the same. [38]



Conclusion

"We are all different, our genes are different (although marginally), we all develop differently, we are all built differently and our life experiences are all different" – *The Song of the Cell, Siddhartha Mukherjee.*

Precision health and precision medicine are not new concepts as we have tailored therapy to treat increasingly smaller populations but to date, we have not consistently used the more advanced tools and technologies now available, as they have not been publicly funded.

Those advanced technologies including genomics, proteomics, metabolomics and bioinformatics are used to analyse large sets of data to make personalised health care decisions.

Precision health informs risk stratification, prevention, diagnosis and treatment decisions.

For our population to benefit from a move to precision health and precision medicine we must remain very aware of ethnic disparity in breast cancer prevalence and survival within NZ, with Māori and Pasifika women experiencing worse outcomes and the need to address rather exacerbate this issue.

As stressed throughout this paper to gain precision oncology benefits for New Zealanders we must better understand our population and investigate whether social determinants of health including access to care and treatments are causing these disparities or biological differences not yet understood.

Is using transcriptomics, proteomics, multi-omics different from using tests that have been used in the clinic for years?

We can only imagine that with significant investment happening in the multi-omics field now and over the next 10 years there will be significant advancement and so we suggest for our population we need to commit to this now, as well as into the future because as we have seen with genomic assays and risk stratification tools, that if these multiomic assays are not validated on our population (through trials and research) inequity will again grow.

Breast Cancer Aotearoa Coalition wants and encourages New Zealand's move towards genomic testing and to begin to recognise that this is a preventative precision health strategy that will positively improve our health outcomes. Countries such as the UK and Australia understand the

value provided by genomic testing and the research and therapies it drives and are assertive in its use as well as the guidance and support required.

There is a need for consumer and community input, education and socialisation regarding these issues so that people may understand the positive outcomes to be gained from genomic testing and precision health, while also being realistic that some may gain more than others.

There is a steady de-escalation occurring in surgery, systemic treatment and radiotherapy, but this progress must be guided by a deeper understanding of the disease and its prognosis in individual patients.

Increased use of artificial intelligence, big data, and digital transformation in breast cancer management will enable us to better tailor treatment to each individual patient. Stratifying patients based on biomarkers in their breast cancers is one approach. Te Rehita Mate Utaetae Breast Cancer Foundation National Register could provide a means to model such improvements especially now that data is gathered nationally.

To progress we therefore need to work with models relevant to our unique population and to do so put building blocks in place which include confidently moving from a dedicated Population Health approach to one that increasingly incorporates Precision Health including Precision Medicine.

This will be made possible by addressing barriers enabling progress at a legislative, policy, leadership, cultural/ diversity, operational, technology and infrastructure level and investing in research and trials.

These actions will be dependent on putting in place budgets, systems and tools that will enable us to build capability and capacity to transform, over time, what is possible to optimise quality of life and health outcomes for our population. We see the establishment of an inclusive Precision Health 'think tank' as described in Project 4 as needed to ensure a connected, innovative precision health system.

Over recent years we have been slow to act in New Zealand and we need to acknowledge that there are consequences to not acting and that will continue unless we adopt a precision health and precision medicine approach over the next 10 years.

As consumers we want clinicians, researchers, scientists and policy makers alongside us with equal ambition to make such improvements.

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Appendix 1

Genomic discrimination — The need for a legislative response

By Laura O'Gorman KC[1]

27 October 2022

Overview

1. This paper addresses the international response to issues of discrimination based on genetic information, particularly for insurance purposes. Following best practice overseas, it recommends the development and introduction of legislation in New Zealand to address the problem of genomic discrimination.

2. There is substantial public benefit from encouraging people to take genetic tests. Broadly speaking, genetic information is used:

   (a) to facilitate the early detection of illnesses and improve the opportunity to achieve better health outcomes, including through earlier preventative interventions and/or targeted therapy;

   (b) to develop more effective, and less harmful, medicine and therapy; and

   (c) to aid research of illnesses.

3. However, without adequate legal protections around use of genetic information, third parties such as employers and insurers can discriminate against those who are, or are seen to be, genetically predisposed to diseases.[2] Studies show that the risk of discrimination deters individuals from taking genomic tests or participating in genomics research,[3] thus denying society of the public benefit of testing.

4. These issues have been managed overseas by specific legislation or self-regulation (industry codes), some of which is summarised below.[4] Despite the issues being identified more than 20

[1] I wish to acknowledge the valuable assistance of Augustine Choi (barrister at Bankside Chambers) for researching the issues and assisting with the preparation of this paper.

[2] See for example Australian Law Reform Commission *Essentially Yours: The Protection of Human Genetic Information in Australia* (ALRC 96, March 2003) at ch 9; Jane Tiller and others "Genetic discrimination by Australian insurance companies: a survey of consumer experiences" (2020) 28 European Journal of Human Genetics 108-113, available at <www.nature.com>.

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[4] See a 2010 paper examining the position taken in 47 different countries: Y Joly, M Braker and M Le Huynh "Genetic discrimination in private insurance: global perspectives" (2010) 29 *New Genetics and Society 351*, available at <doi.org/10.1080/14636778.2010.528189>. An international comparative analysis is also contained in the report of the Parliamentary Joint Committee on Corporations and Financial Services, Parliament of Australia, *Life Insurance Industry*, Report (2018), Chapter 9 Genetic Information.

years ago,[5] New Zealand currently lags behind to a significant degree, because it has failed to take any specific responsive measures.

Genetic Testing – Trade-offs and economics

5. The advantages of genomic testing are discussed in the New Zealand Medical Journal article "Genomic discrimination in New Zealand health and life insurance. AGenDA: Against Genomic Discrimination in Aotearoa" (11 March 2022).[6]

   (a) Genomic testing to detect risk conditions can save lives through early preventative interventions and/or improved targeted therapy (which in turn assists more effective and efficient public health spending).

   (b) For people at risk of genetic conditions, choosing not to be tested (for fear of discrimination) may have serious direct health impacts,[7] again impacting adversely on public health burdens.

   (c) Such fear can also deter recruitment into genomic research studies critical to understanding disease, developing prevention/therapies, and improving patient outcomes — another missed opportunity of reducing the overall public health burden.

6. Correspondingly, the moral reasons for addressing genomic discrimination include:[8]

   (a) It is unfair to discriminate against someone based on such an immutable, personal, and uncontrollable trait as one's genetic make-up, in the same way it is unjust to discriminate based on race or gender.[9]

   (b) Discrimination could lead to a so-called genetic underclass—a group of people unable to access insurance or other parts of society because of their genes.[10] The popular film *Gattaca* (1997) explored these issues.

7. Insurers may argue that lack of access to information about genetic risk, or inability to use the information, could lead to unfair pricing constraints and inefficiencies. On the other hand, existing literature indicates that there is little risk of overall detriment to insurers:[11]

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[5] See Pamela Jensen "Genetic Privacy: The Potential for Genetic Discrimination in Insurance" [1999] VUWLawRw 21; (1999) 29(2) Victoria University of Wellington Law Review 347. As the author identifies in the conclusion, those interested would include the Human Rights Commission, the Health and Disability Commissioner, the Privacy Commissioner, the Ministry of Health, geneticists, medical ethicists, lawyers and the insurance industry.

[6] Andrew Shelling and others "Genomic discrimination in New Zealand health and life insurance. AGenDA: Against Genomic Discrimination in Aotearoa" (2022) 135 New Zealand Medical Journal 7, available at <journal.nzma.org.nz> [**Shelling and others "Genomic discrimination in New Zealand"**].

[7] Mark Rothstein "Time to end the use of genetic test results in life insurance underwriting" (2018) 46 J Law Med Ethics 794, available at <doi.org/10.1177%2F1073110518804243> [**Rothstein "Time to end the use of genetic test results"**].

[8] Anya Prince and others "Genetic testing and insurance implications: Surveying the US general population about discrimination concerns and knowledge of the Genetic Information Nondiscrimination Act (GINA)" (15 July 2022) International Insurance Society <www.internationalinsurance.org>.

[9] Anya Prince "Insurance Risk Classification in an Era of Genomics: Is a Rational Discrimination Policy Rational?" (2017) 96 Neb Law Rev 624, available at <www.ncbi.nlm.nih.gov>.

[10] Eric Mills Holmes "Solving the Insurance/Genetic Fair/Unfair Discrimination Dilemma in Light of the Human Genome Project" (1997) 85 *Kentucky Law Journal* 503, available at <uknowledge.uky.edu>; and Angus Macdonald and Fei Yu "The Impact of Genetic Information on the Insurance Industry: Conclusions from the 'Bottom-Up' Modelling Programme" (2011) 41 *Astin Bulletin* 343, available at <www.actuaries.org>.

[11] Dexter Golinghorst and others "Anti-selection & Genetic Testing in Insurance: An Interdisciplinary Perspective" (2022) 50 J Law Med Ethics 139, available at <papers.ssrn.com>; and Shelling and others "Genomic discrimination in New Zealand", above n 6, at 8, referring to: Cathleen Zick and others "Genetic testing, adverse selection, and the demand for life insurance"

(a) Insurers argue that if applicants are not required to disclose predictive genetic information, those at higher risks could apply for greater policy coverage without insurers being able to assess risk and set appropriately higher premiums, a concept known as "anti-selection" (resulting from information asymmetry).[12] They say that anti-selection may reduce available coverage levels and lead to increased prices for all consumers, even those without genetic predispositions. If they set prices according to the average risk in the population, they could over-attract higher-risk customers, which may create a need to raise premiums. If relatively better risks then drop out of the insurance market, premiums could rise anew, with the potential that in the end only very high-risk types will be insured.[13] If the economic impact is too dire, financial concerns may outweigh genetic privacy and non-discrimination concerns; if it is minimal, regulation may be justifiable to promote human rights and public health.[14]

(b) However, the actuarial and economic models and studies do not suggest wide-spread or material anti-selection effects related to genetic testing.[15] To the contrary, both the insurers and society more generally are likely to benefit from reduced health costs arising from early preventative interventions and/or improved targeted therapy.

New Zealand's current legal framework

8. In the absence of legislation addressing the specific issue of genomic discrimination, existing legislation and the general law will apply to some aspects of how genetic information may be accessed and used:[16]

(a) General legal concepts of confidentiality and the tort of invasion of privacy[17] may apply, to give some protections from disclosure and misuse of private health information.

(b) In addition, New Zealand has legislation regulating the circumstances in which medical or health information can be acquired and disclosed to a third party. This is outlined in the *Health Act 1956,* which cross-refers to the *Privacy Act 2020* and the Health

(2000) 93 Am J Med Genet 29; Jane Tiller and Martin Delatycki "Genetic discrimination in life insurance: a human rights issue" (2021) 47 Journal of Medical Ethics 484, available at <dx.doi.org/10.1136/medethics-2021-107645>; Rothstein "Time to end the use of genetic test results", above n 7; Mark Rothstein and Kyle Brothers "Banning Genetic Discrimination in Life Insurance — Time to Follow Florida's Lead" (2020) 383 N Engl J Med 2099, available at <doi.org/10.1056/nejmp2024123>; Angus Macdonald "The Actuarial Relevance of Genetic Information in the Life and Health Insurance Context" (July 2011) Office of the Privacy Commissioner of Canada <www.priv.gc.ca>; and Michael Hoy and Maureen Durnin "The Potential Economic Impact of a Ban on the Use of Genetic Information for Life and Health Insurance" (March 2012) Office of the Privacy Commissioner of Canada <www.priv.gc.ca>.

[12] Elizabeth Adjin-Tettey "Striking the Right Balance: Does the Genetic Non-Discrimination Act Promote Access to Insurance?" (2021) McGill Journal and Law and Health Vol 14, No 2, 145 at 158, available at <canlii.org>; Dexter Golinghorst and others "Anti-selection & Genetic Testing in Insurance: An Interdisciplinary Perspective" (2022) 50 J Law Med Ethics 139, available at <papers.ssrn.com>.

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[15] See for example Elizabeth Adjin-Tettey "Striking the Right Balance: Does the Genetic Non-Discrimination Act Promote Access to Insurance?" (2021) McGill Journal and Law and Health Vol 14, No 2, 145 at 159 and footnote 51, available at <canlii.org>; Dexter Golinghorst and others "Anti-selection & Genetic Testing in Insurance: An Interdisciplinary Perspective" (2022) 50 J Law Med Ethics 139, available at <papers.ssrn.com>; Jane Tiller and others "Genetic discrimination by Australian insurance companies: a survey of consumer experiences" (2020) 28 European Journal of Human Genetics 108-113, available at <www.nature.com>; and other papers referred to above n 11.

[16] See OECD "Regulatory Developments in Genetic Testing in New Zealand" <www.oecd.org>.

[17] See *Peters v Attorney-General* [2021] NZCA 355, [2021] 3 NZLR 191.

Information Privacy Code 2020. Among other things, health agencies are permitted to disclose genetic information to a third party without consent in circumstances where the information could lessen or prevent a serious threat to the life, health or safety of a person. Section 22C of the Health Act also permits the use of patient information on public health grounds, in circumstances such as authorised requests by officials, including the police.

(c) 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.

(d) Conduct that may be discriminatory ordinarily falls within the scope of the Human Rights Act 1993 (with freedom from discrimination in turn protected under s 19 of the New Zealand Bill of Rights Act 1990).[18] However, the prohibition in s 44 of the Human Rights Act 1993 against refusing to provide goods or services, or treating any person less favourably in connection with the same, by reason of discrimination does not apply to the provision of insurance policies in circumstances where the conduct is reasonable, having regard to the particular circumstances, and based on reasonably reliable actuarial or statistical data, or medical advice or opinion (s 48).

9. Accordingly, none of the above prevents private service providers, such as insurers, from asking for and using genomic test results and using that information to refuse access to the services, or to charge more for them (e.g. higher insurance premiums).

10. 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 (focussed on individual entitlements) are inadequate to protect:[19]

(a) health information as regarded as a *taonga* (treasure) 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).

International approaches to combat genomic discrimination

11. The Universal Declaration on the Human Genome and Human Rights was adopted unanimously and by acclamation at UNESCO's 29th General Conference on 11 November 1997. The following year, the United Nations General Assembly endorsed the Declaration, and Guidelines for the Implementation of the Declaration (1999) were endorsed by the General Conference at its 30th session. Among other things, Article 6 provides:

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[18] See a discussion of the issues from a Human Rights perspective in speech notes of Rosslyn Noonan (Chief Commissioner, Human Rights Commission) and Robert Hallowell (Legal Counsel, Human Rights Commission): Rosslyn Noonan and Robert Hallowell "Never make forecasts, especially about the future" (March 2003), available at <privacy.org.nz>.

[19] See Report of the Royal Commission on Genetic Modification (2001) at pp276, 285 and 326-327, available at <https://environment.govt.nz/publications>; OECD "Regulatory Developments in Genetic Testing in New Zealand" <www.oecd.org>; Waitangi Tribunal *Ko Aotearoa Tēnei, Te Taumata Tuatahi: A Report into Claims Concerning New Zealand Law and Policy Affecting Māori Culture and Identity* (Wai 262, 2011) [Wai 262]; and Tai Ahu, Amy Whetu and James Whetu "Mātauranga Māori and New Zealand's intellectual property regime — challenges and opportunities since Wai 262" (2017) 8 NZIPJ 79.

> No one shall be subjected to discrimination based on genetic characteristics that is intended to infringe or has the effect of infringing human rights, fundamental freedoms and human dignity.

12. Other countries have responded to these commitments and addressed the specific problem of genomic discrimination. The methods used have varied significantly, particularly in the insurance sphere. This section briefly summarises the different approaches.

(i) United Kingdom

13. In the United Kingdom the concern around the impact of genetic information on insurance emerged in the late 1990s.[20] The Association of British Insurers (**ABI**) and the Government adopted a semi-voluntary approach to regulation. A voluntary moratorium (**the Moratorium**) on insurers' use of predictive genetic test results came into effect in 2001. A policy framework agreement (**the Concordat**) on the use of genetic test results in insurance underwriting practices came into effect in 2005.[21] The Concordat and Moratorium were regularly reviewed, updated and extended until their replacement by the voluntary, open-ended, eight-point Code on Genetic Testing and Insurance in 2018 (**the Code**).[22] It is the Code by which members of the ABI have agreed to abide.

14. The Code supplements existing legislation on the use of medical information for insurance (and other purposes), such as the Data Protection Act 2018, which sets out responsibilities of controllers of data, and the Access to Medical Reports Act 1988, which governs how requests for medical information should be made and the need for consent.

15. The Code prohibits insurers from requiring or pressuring an applicant to take a predictive or diagnostic genetic test[23] to obtain insurance.[24] However insurers can ask for diagnostic genetic test results, and the results can be taken into account by insurers.

16. The Code allows insurers to ask for, and take into account, predictive genetic test results **only** for specific conditions[25] and for specific high-value policies, being life insurance for over £500,000, critical illness insurance for over £300,000 and income protection for over £30,000 per annum.[26] This means predictive genetic test results cannot be sought or considered for travel insurance, health insurance, and motor vehicle insurance, for example. Insurers cannot ask for the results of a predictive genetic test results: taken after the insurance cover has started for the duration of that cover, of another person, or obtained exclusively in the context of scientific research.[27]

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[20] SC Davies *Annual Report of the Chief Medical Officer 2016: Generation Genome* (Department of Health, London, 2017) at chapter 15, page 3.
[21] Association of British Insurers and HM Government "Concordat and Moratorium on Genetics and Insurance" (2014) at [37].
[22] Association of British Insurers and HM Government "Code on Genetic Testing and Insurance" (October 2018) at 5 and 7–8 [**2018 UK Code**].
[23] "*Diagnostic genetic tests*" are defined as the kind of genetic tests that "*confirm or rule out a diagnosis based on existing symptoms, signs or abnormal non-genetic test results which indicate that the condition in question may be present*". "*Predictive genetic tests*" are defined as those that "*predict a future risk of disease in individuals without symptoms of a genetic disorder*": 2018 UK Code at 4.
[24] 2018 UK Code at 7 (Commitment 1).
[25] The only one currently being Huntington's disease.
[26] 2018 UK Code at 7 (Commitment 2).
[27] 2018 UK Code at 7 (Commitment 3).

17. If a predictive genetic test result is provided accidentally or voluntarily, an insurer may take it into account if it is to the applicant's benefit.[28] However if the result is unfavourable then the insurer must ignore the result unless the Code otherwise allows the insurer to take it into account.[29]

18. The Code requires relevant insurers to be transparent with applicants and to report their compliance with the Code annually and to maintain a complaints procedure.[30]

(ii) Australia

19. Australia has a mixed legislative and semi-voluntary approach to the regulation of health-related insurers. Legislation governs the position with health insurance while a semi-voluntary model still applies for life insurance products.

20. The Private Health Insurance Act 2017 (Cth) (**PHIA**) prohibits health insurers from using genetic information to discriminate against customers. It does so through its broad definition of "*improper discrimination*", which includes "*discrimination that relates to … (a) the suffering by a person from a chronic disease, illness or other medical condition … (e) any other characteristic of a person … that is likely to result in an increased need for hospital treatment or general treatment*".[31] The Disability Discrimination Act 1992 (Cth) (**DDA**) does something similar. It defines disability to include disabilities that not only presently exist but "*may exist in the future (including because of a genetic predisposition to that disability)*" and sets out an array of areas in which it is not permissible to discriminate, including in work and in the provision of goods, services and facilities.[32]

21. However life insurers are not prohibited by legislation from discriminating using genetic information.[33] The 2018 Parliamentary report on the life insurance industry (**the Australian LII Report**) recommended further consideration of a moratorium on life insurers using predictive genetic information (except where the consumer provides such information to show they are *not* at risk), and implementing an interim moratorium.[34] The Australian LII Report also recommended that if a moratorium goes ahead, the government should consider whether legislation is required.[35]

22. The moratorium bears similarities to the Code in the United Kingdom.

23. In 2019, life insurer members of the Financial Services Council (**FSC**), an Australian industry body to which all life insurers currently belong, agreed to a five-year limited moratorium on the use of genetic test[36] results by life insurers (**the Australian Moratorium**).[37] The Australian Moratorium covers applicants for individually underwritten life insurance with an FSC member.[38] Regardless of the amount of cover, life insurers will not ask or encourage applicants:

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[28] For example if it helps to rule out a risk which was otherwise suggested by family history.
[29] 2018 UK Code at 8 (Commitment 6).
[30] 2018 UK Code at 8 (Commitment 7).
[31] Private Health Insurance Act 2017 (Cth), s 55-5.
[32] Disability Discrimination Act 1992 (Cth), s 4 and pt 2.
[33] See for example the exemption under the Disability Discrimination Act 1992 (Cth), s 46.
[34] Parliamentary Joint Committee on Corporations and Financial Services "Life Insurance Industry" (Canberra, March 2018) at [9.98] and [9.100].
[35] Parliamentary Joint Committee on Corporations and Financial Services "Life Insurance Industry" (Canberra, March 2018) at [9.101]
[36] Genetic test is defined as one "*which examines a person's chromosomes or DNA*": Financial Services Council "FSC Standard No 11: Moratorium on Genetic Tests in Life Insurance" (21 June 2019) at [6.1].
[37] Financial Services Council "FSC Standard No 11: Moratorium on Genetic Tests in Life Insurance" (21 June 2019).
[38] Financial Services Council "FSC Standard No 11: Moratorium on Genetic Tests in Life Insurance" (21 June 2019) at [2.1].

(a) to take a genetic test during the application or underwriting process, or

(b) to disclose the results of a genetic test taken as part of a medical research study if the results are not provided, or the applicant has asked not to receive the results.[39]

24. However as in the United Kingdom, life insurers may ask for and use the results of a genetic test (during the application process[40]) if the total amounts of cover the applicant seeks is more than $500,000 of death cover, $500,000 of total permanent disability cover, $200,000 for trauma/critical illness cover, and $4,000 a month of income protection cover.[41] Life insurers may also take into account a favourable genetic test that an applicant chooses to disclose and preventive treatment being undertaken to reduce the risk of inherited disease(s).[42]

25. Under the Australian Moratorium, life insurers may still ask applicants to disclose, and take into account, any diagnosis of a condition even if it resulted directly or indirectly from a genetic test.[43]

26. Australia's Financial Services Council recently released its updated life insurance Code of Practice which will come into effect in July 2023.[44] The Australian Moratorium is retained in Appendix A (with the same financial thresholds). It currently has an end date of 30 June 2024,[45] but this will be reviewed during 2022 with a view to extending that date.[46] Relevant to that review is a funded project (yet to be completed) to monitor the impact of the Australian Moratorium on genetic testing and life insurance.[47]

(iii) Canada

27. Canada has opted for a purely legislative approach.

28. In 2017 the federal Parliament enacted the Genetic Non-Discrimination Act. The Act is notable for its brevity and breadth. It has just 11 sections. The Act provides a general prohibition against any person from requiring a person to take a genetic test or to disclose genetic test results as a condition of (a) providing goods or services to, (b) entering into or continuing a contract or agreement with, or (c) offering specific conditions in a contract or agreement with, the person.[48] A person cannot collect, use or disclose the results of a genetic test of someone they are providing goods or services to, or entering or continuing an agreement with, unless they have the latter's written consent.[49] Contravention of the Act's prohibitions are serious offences with maximum penalties of $1,000,000 and five years' imprisonment.[50]

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[39] Financial Services Council "FSC Standard No 11: Moratorium on Genetic Tests in Life Insurance" (21 June 2019) at [3.2].
[40] See also Financial Services Council "FSC Standard No 11: Moratorium on Genetic Tests in Life Insurance" (21 June 2019) at [3.6].
[41] Financial Services Council "FSC Standard No 11: Moratorium on Genetic Tests in Life Insurance" (21 June 2019) at [3.3].
[42] Financial Services Council "FSC Standard No 11: Moratorium on Genetic Tests in Life Insurance" (21 June 2019) at [3.5].
[43] Financial Services Council "FSC Standard No 11: Moratorium on Genetic Tests in Life Insurance" (21 June 2019) at [3.1].
[44] Available at <www.fsc.org.au>.
[45] Financial Services Council *Life Insurance Code of Practice 2023*, Appendix A, A.1(e).
[46] Financial Services Council *Life Insurance Code of Practice 2023*, Appendix A, A.3(a).
[47] The Australian Government's *Genomic Health Futures Mission* has made a $500.1 million investment in genomic medicine research - see <https://www.health.gov.au/initiatives-and-programs/genomics-health-futures-mission>. The monitoring project is listed in Appendix A, Implementation Plan Priority Area 3.1 (AU$500,000, Monash University) – see Jane Tiller, Ingrid Winship, Margaret Otlowski and Paul Lacaze *Monitoring the genetic testing and life insurance moratorium in Australia: a national research project*, available at <https://doi.org/10.5694/mja2.50922>.
[48] Genetic Non-Discrimination Act 2017 (Can), ss 3 and 4.
[49] Genetic Non-Discrimination Act 2017 (Can), s 5.
[50] Genetic Non-Discrimination Act 2017 (Can), s 7.

29. The Act's general prohibition does not apply to health care practitioners providing health services, or to medical, pharmaceutical or scientific researchers.[51]

30. The Act also amends the Canada Labour Code to protect employees from being required to undergo or to disclose the results of a genetic test, and provides employees with other protections related to genetic testing and test results, and the Canadian Human Rights Act to prohibit discrimination on the ground of "*genetic characteristics*". Discrimination on the basis of genetic characteristics includes discrimination on the grounds of a refusal to take or disclose the results of a genetic test.[52]

(iv) United States of America

31. The United States has also opted for a legislative approach in relation to health insurance.

32. Legislative efforts to prohibit genetic discrimination by health insurers (and employers) began in the 1990s. In 2008 and 2010 Congress passed the Genetic Information Nondiscrimination Act 2008 (**GINA**) and the Affordable Care Act 2010 (**ACA**).

33. By amendments to existing legislation,[53] GINA prohibits health insurers from requesting genetic testing or genetic information, and from discriminating based on genetic information, in relation to determining eligibility for benefits, coverage, and premiums/contributions, and any other activity related to the creation, renewal, or replacement of a contract of health insurance or health benefits.[54] The amendment to the Health Insurance Portability and Accountability Act (**HIPAA**) regulations confirms genetic information as health information protected by the HIPAA's Privacy Rule, which protects the privacy of all individually identifiable health information and controls their use and disclosure.[55]

34. "*Genetic information*" includes information about genetic tests of the individual and their family members, as well as manifested diseases in family members. It also includes any request for or receipt of genetic services or participation in clinical research that includes genetic services by the individual or their family members.[56] A "*genetic test*" generally means an analysis of human DNA, RNA, chromosomes, proteins or metabolites, that detects genotypes, mutations, or chromosomal changes.[57]

35. The ACA supplements the GINA regime and requires insurance issuers to provide coverage for all individuals who request it. Insurers cannot refuse coverage for, or increase costs to, individuals because of pre-existing conditions.

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[51] Genetic Non-Discrimination Act 2017 (Can), s 6.
[52] Genetic Non-Discrimination Act 2017 (Can), s 10.
[53] The Employee Retirement Income Security Act 1974, Public Health Service Act, Internal Revenue Code 1986, Social Security Act, and regulations under the Health Insurance Portability and Accountability Act [**HIPAA**].
[54] See for example Genetic Information Nondiscrimination Act 2008, sec 101(d), definition of "underwriting purposes" [**GINA**].
[55] National Human Genome Research Institute "Genetic Discrimination" (retrieved 12 September 2022) <www.genome.gov>; and Department of Health and Human Services "Summary of the HIPAA Privacy Rule" (last revised May 2003) <hhs.gov>.
[56] See for example GINA, sec 101(d), definition of "genetic information".
[57] See for example GINA, sec 101(d), definition of "genetic test". A genetic test does not include however "*an analysis of proteins or metabolites that does not detect genotypes, mutations, or chromosomal changes; or … an analysis of proteins or metabolites that is directly related to a manifested disease, disorder, or pathological condition that could reasonably be detected by a health care professional with appropriate training and expertise in the field of medicine involved.*"

36. GINA protections do not apply to long-term care insurance, life insurance, or disability insurance. A few states extend protections to these areas but there is no federal legislation to prevent genetic discrimination in these areas.[58]

Comparison of the different approaches

37. The different approaches to tackling the problem of genomic discrimination in health and life-related insurance can be compared by considering how they deal with several common issues.

(i) Different types of insurance

38. Only Canada has adopted a uniform approach to genomic discrimination in relation to both health insurance and life insurance (as well as in most other spheres of life). The scheme in the United Kingdom is similar in that it treats health and life insurance essentially the same. With the exception of a few states, the United States has taken no steps towards preventing genomic discrimination in life insurance. And in Australia, a very different approach is taken to life insurance than to other insurances.

39. There is no clear rationale not to have rules against genomic discrimination in relation to both health insurance and life insurance. The concern about deterring what would otherwise be useful testing applies equally whether an applicant or potential applicant is looking at either type of insurance.

(ii) Mandatory legislation or semi-voluntary scheme

40. Canada, in relation to both health and life insurance, and Australian and the United States in relation to health insurance, have adopted legislative schemes. Meanwhile the United Kingdom and the life insurance industry in Australia have adopted semi-voluntary schemes — in the sense of binding, industry-agreed rules.

41. England's Chief Medical Officer's annual report on genomics in 2016 supported the flexible semi-voluntary regulatory structure comprised at the time by the Concordat and Moratorium. In that report writers' view the kind of regulatory structure adopted was better able than legislation to cope with the fast moving technology. It was also better able to adapt to the insurance industry's underwriting principles.[59]

42. On the other hand, competition issues might arise with any attempt to implement a solution via voluntary industry schemes. Section 30 prohibits horizontal contracts or arrangements that contain or give effect to a "cartel provision". That phrase in turn is defined widely in s 30A to include a provision that fixes, controls or maintains the price for services or any discount, allowance, rebate or credit. There is no necessity for there to be an agreement or understanding that an absolute position as to price must be maintained for there to be anti-competitive conduct. All that is required is an agreement that will have an effect on price.[60] Therefore there is a risk that insurance industry discussion about the potential price impacts of genetic information (and how that should be addressed) is unsafe territory.

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[58] National Human Genome Research Institute "Genetic Discrimination" (retrieved 12 September 2022) <www.genome.gov>; and JD Tenenbaum and KW Goodman "Beyond the Genetic Information Nondiscrimination Act: ethical and economic implications of the exclusion of disability, long-term care and life insurance" (2017) 14 Per Med 153.

[59] SC Davies *Annual Report of the Chief Medical Officer 2016: Generation Genome* (Department of Health, London, 2017) at chapter 15, page 7.

[60] See *Lodge Real Estate Ltd v Commerce Commission* [2020] NZSC 25, [2020] 1 NZLR 238 at [139]–[146]: "What this means is that the Commission was required to prove only that the arrangement had the purpose or effect of restraining a freedom that would otherwise have existed as to the price to be charged": at [146].

43. Voluntary codes are also subject to criticisms about lack of oversight, compliance monitoring and enforcement.

(iii) Financial limits to application of restrictions

44. The report by England's Chief Medical Officer noted that the different treatment depending on policy limits reflects the different requirements insurers have for underwriting insurance contracts based on the size of the sum insured. On the limits used in the Concordat and Moratorium (which are the same as those in the Code), the estimate was that more than 95% of insurance customers would not need to disclose genetic test results.[61]

45. Similar financial limits apply under the Australian Moratorium. Given the international nature of the insurance industry, it is expected this has been for the same reason.

46. An earlier version of the Canadian bill had exemptions in respect of high-value insurance policies,[62] but these did not remain in the legislation as enacted.

(iv) Amendments to existing rules/legislation or new rules/legislation

47. In Australia the changes to restrictions in relation to health insurance have been achieved through amendments to existing legislation and broadening existing general anti-discrimination rules in the PHIA and DDA. In contrast Canada simply passed a standalone regime within minimal amendments to existing legislation. In doing so it ostensibly left any remaining inconsistencies to be interpreted by the Courts, which is arguably not very efficient.

(v) Test results and family history

48. In Canada, the United Kingdom and Australia, the protected information are the results of genetic tests. In Canada that is defined as "*a test that analyzes DNA, RNA or chromosomes for purposes such as the prediction of disease or vertical transmission risks, or monitoring, diagnosis or prognosis*". The Australian Moratorium uses a simpler definition of "*a test which examines a person's chromosomes or DNA*".

49. Family medical histories, explicitly protected in the United States, appears not to be protected in Canada, the United Kingdom or Australia.[63]

(vi) Research carve-out

50. All the legislation examined have exemptions for use of genetic information for medical and scientific research purposes. Whether this is necessary depends on the breadth and language of the legislation, if legislation is amended or new legislation introduced.

(vii) Diagnostic genetic tests and predictive genetic tests

51. In the United Kingdom and Australia, use of diagnostic genetic tests by insurers is distinguished from the use of predictive genetic tests, with the former remaining essentially permissible.[64] In Canada all genetic tests are lumped together in relation to whether they can be used by insurers.

52. Predictive genetic tests may be seen as a greater concern when considering genomic discrimination, due to the uncertainty of whether the diseases the risk of which are predicted

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[61] SC Davies *Annual Report of the Chief Medical Officer 2016: Generation Genome* (Department of Health, London, 2017) at chapter 15, page 7.

[62] *Reference re Genetic Non-Discrimination Act* [2020] SCC 17 at [58] and [61].

[63] Although in Australia, genetic discrimination in health insurance based on family medical history could be in breach of the PHIA and DDA.

[64] 2018 UK Code; and Financial Services Council "FSC Standard No 11: Moratorium on Genetic Tests in Life Insurance" (21 June 2019) at [3.1].

would actually appear. It is not clear why diagnostic genetic tests should be less protected. Such tests (conducted when there are symptoms or signs of disease) can help to confirm or rule out a diagnosis, and to help identify the best therapy and medicine.

Legal and other challenges

53. Opponents of the Canadian legislation before it was passed were concerned about the eventual increase in premiums. One group considered that a self-imposed prohibition on use of genetic test information for life insurance applications up to $250,000 would be enough for about 85 per cent of applications not to require disclosure of genetic information.[65]

54. After Canada passed the Genetic Non-Discrimination Act 2017, Quebec made a constitutional challenge, which ultimately failed in the Supreme Court of Canada.[66] The challenge is irrelevant to the situation in New Zealand as it was founded on the Canadian Constitution and its division of law-making powers between the federal and provincial legislatures.

55. It is notable that the United States's GINA was passed 414–1 in the House of Representatives and 95–0 in the Senate.

Recommendation

56. Of the range of options, the general Canadian legislative approach appears the most attractive:

    (a) The legislation is comprehensive, accessible and clear. It avoids arbitrary thresholds and distinctions between different types of insurance, and different types of genetic tests. These should be avoided, unless reliable empirical and economic data can be provided to support such distinctions.

    (b) Despite action taken in other jurisdictions years ago, New Zealand's insurance industry has not been pro-active with self-regulation. In any event, such action could be problematic on competition law grounds, and voluntary codes are subject to criticisms about lack of oversight, compliance monitoring and enforcement.

    (c) Legislation is an appropriate step for New Zealand to take, consistent with the values underlying the *Universal Declaration on the Human Genome and Human Rights*.[67]

    (d) The *Te Ao* Māori perspective should be considered, including whether any definitions used in the proposed legislation will be broad enough to protect the collective *taonga* of genetic information.

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[65] Parliamentary Joint Committee on Corporations and Financial Services "Life Insurance Industry" (Canberra, March 2018) at [9.23].
[66] *Reference re Genetic Non-Discrimination Act* [2020] SCC 17.
[67] *Universal Declaration on the Human Genome and Human Rights* UNESCO Res (11 November 1997).

Laura O'Gorman KC

BARRISTER

ddi:+64-9-200 1501 | m:+64-21 313 653

e: laura@logorman.com | w: www.logorman.com