Polygenic Score Incubator Project

What do we need to know to implement polygenic scores into Australian healthcare?

Priorities for research

August 2022

Australian Genomics

CONTENTS

This work was commissioned by Australian Genomics and led by Professor Andrew Wilson and Mary-Anne Young. The report was prepared by the Project Working Group under the guidance of the Project Strategy Group (PGS research and clinical experts).

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1. EXECUTIVE SUMMARY

Polygenic disorders (also called complex disorders or diseases) are those where multiple genetic variants influence disease development, in addition to other non-genetic factors such as lifestyle and environmental factors.

The use of polygenic scores (PGS) in healthcare is an emerging field with the potential to inform and individualise healthcare and improve health outcomes. PGS research from Australia and around the world is ever-increasing, from discovery studies to implementation trials, for both individual clinical care and population health.

Like many countries, Australia is uncertain about how best to integrate and utilise PGS in an equitable and cost-effective way. Currently, the use of PGS primarily occurs in the research environment as well as limited availability from user-pays private companies. Whilst PGS hold promise to contribute to the health of individuals and populations there are significant challenges for widespread use in Australian healthcare.

Aim and scope

The aim of this *Australian Genomics Polygenic Score Incubator Project* is to provide recommendations to the Australian Government Medical Research Futures Fund (MRFF) about research priorities to support PGS implementation in the Australian health context.

This report describes the current state of PGS research and applications in clinical and public health practice in Australia and internationally and the views of experts working on various aspects of PGS research and clinical application. The focus of the report is research that can inform implementation.

What is a polygenic score?

A PGS (also called polygenic risk score or PRS) is a single score derived by adding together genomic variants (single nucleotide polymorphisms, or SNPs) that have been found in genome-wide association studies (GWAS) to be associated with a specific disease, weighted for their level of effect. Each of these SNPs on their own have a small effect but combined they can indicate an individual's risk of developing a disease or other health state such as response to therapies. If an individual's PGS is high relative to others in the population, it suggests preventive action or a tailored therapy. PGS are used to estimate risk for common complex diseases such as cancers and heart disease. Given these conditions are due to both genetic and non-genetic factors, and PGS do not measure the entire genetic contribution to a disease, they can be combined with other non-genetic risk factors in a combined risk tool.

The characteristics of a good PGS include:

- Prediction accuracy: this depends on the genetic contribution to disease risk, the SNPs included in the PGS, and the statistical methods for PGS calculation
- Transferability: the PGS should be transferable across populations with different genetic ancestries (depends on ancestries included in the GWAS data and statistical methods used to generate the PGS)

- Ease of interpretation: health professionals who are not experts on PGS methods need to be able to interpret the information
- Reproducibility: a PGS developed for a specific heath condition should be reproducible by others (this depends on availability of the data used to develop the PGS).

A good PGS should contribute information over and above that given by existing risk factors.

Potential uses of PGS

PGS are potentially useful (in some cases already in use), to:

- inform population screening and provide personalised risk estimates for screening or preventive treatments/interventions (also in combination with environmental and biomarker risk factors)
- aid in disease diagnosis (e.g., to distinguish between type 2 and type 1 diabetes)
- provide information that can modify risk for a person carrying a pathogenic genetic variant for a high risk of disease (referred to as a Mendelian disorder).
- help with treatment decisions/pathways (e.g., to inform use of statin therapy to reduce risk of CVD) and guide therapeutic interventions (the use of PGS in pharmacogenomics is not yet well developed but is under active investigation).

Project

This report draws on a scan of the current PGS landscape in Australia and internationally to identify the major networks and resources for PGS research, and an examination of the literature to identify the main studies and current thinking around research and implementation. We sought advice from national and international experts and conducted a qualitative interview survey (n=13) and a workshop of national experts (n=31) to identify priorities to advance PGS research that will inform future implementation and drive clinical translation of PGS in the Australian health system.

Challenges for PGS implementation

Expert reviews of PGS from around the world generally agree on the varied challenges for moving PGS from research to widespread clinical translation. These include:

- Test methodology: Developing test evaluation frameworks for PGS to provide evaluators with a consistent methodology for evaluation of PGS, from the laboratory test to clinical use
- Regulation: Determining the appropriate regulatory oversight to ensure the PGS is safe and effective in the clinical contexts in which it will be used and to prevent non-ethical use
- Demonstrating the clinical utility of PGS in a range of specific clinical contexts (e.g., improved clinical decision-making and health outcomes, more effective screening programs)
- Managing potential harms from PGS information
- Developing best practice guidelines for a range of health professionals
- Developing appropriate evidence-based education for health professionals and the public
- Managing data and health information storage and access

- Laboratory resources for large-scale genomic testing and PGS reporting systems
- Ensuring that health disparities are not exacerbated by inequitable access to PGS tests
- Identifying funding sources for various PGS clinical and population health uses (health technology assessment and applications for public funding).

The current landscape of PGS (Australia and internationally)

Health conditions under active investigation for PGS implementation

The use of PGS in estimating risk or defining management of some common conditions is further along the path to implementation than others, for reasons including: the prevalence and heritability of the condition; existing screening protocols (either at a population level or in primary care); a well-developed PGS test (clinical validity); and existing interventions for improved health outcomes.

The main health conditions under active investigation and showing promise for implementation are:

- Breast cancer (for risk-stratified screening; personalised risk estimates in familial breast cancer; guiding risk-reducing interventions; differentiating between subtypes of breast cancer)
- Cardiovascular disease, mainly coronary artery disease (CAD) (for personalised risk estimates incorporated into existing risk tools; guiding statin therapy for primary or secondary prevention)
- Other cancers: melanoma (for targeted screening/surveillance); colorectal cancer (for risk-stratified screening); prostate cancer (to improve predictive value of PSA testing)
- Diabetes: type 1 diabetes (for neonatal/infant screening and intervention to prevent or delay onset); type 2 diabetes PGS are not as well advanced but are being investigated.
- Glaucoma (for risk of developing glaucoma to inform early screening and diagnosis)
- Mental health disorders (for facilitating diagnosis and prognosis; guiding treatment decisions).

The international landscape

Various networks, consortia and organisations involved in PGS research (from GWAS and PGS development to implementation studies) were identified, particularly from the UK, Europe and USA and multinational networks. Some of these are running large cohort studies that involve genomic testing, as well as collecting clinical and other health data, for use by researchers testing PGS implementation (e.g., *Our Future Health* in the UK; *All of Us Research Program* in the USA). Other networks aim to facilitate effective research across groups and/or countries, such as the UK *PHG Foundation* (leading think-tank on evaluation and implementation of PGS); and the *Polygenic Risk Score Task Force of the International Common Disease Alliance (ICDA).* There are also a range of databases and tools to aid PGS development and research

The main large randomised or non-randomised trials currently underway are in breast cancer (7 trials from Europe, USA, Spain, Singapore, Canada), CAD, type 1 diabetes (infant screening) and one involving PGS for multiple conditions (CAD, type 2 diabetes, atrial fibrillation, colorectal cancer, prostate or breast cancer).

Studies focused on the understanding of PGS, behaviour change and public and professional views of PGS indicate that the evidence for health or preventive behaviour change based on PGS information

is lacking and barriers to access and uptake have been identified for health professionals and the public, including lack of knowledge of PGS.

In summary, extensive research is happening around the world to gather evidence to inform implementation. However, a variety of challenges remain and the need for coordinated efforts has been echoed by many experts in the field.

The Australian landscape

Researchers from across Australia are making valuable contributions to the PGS field, from basic science research (GWAS studies and PGS development), to clinical, psychosocial and health communication research.

There are few formal networks in Australia currently working in PGS research but there are many research collaborations across states and institutions.

Australian researchers are making concerted efforts to include diverse ancestries in GWAS studies to better reflect the Australian population and to extend the clinical applicability of PGS to people of non-European ancestry (a widely discussed limitation of current PGS).

There are few large trials currently in Australia, but some may be in the planning stages.

Australian researchers are making significant contributions to assessing the psychosocial aspects of PGS in breast cancer and melanoma, and public and health professionals' understanding and views on PGS in a variety of conditions. Health economic studies are part of new research programs.

In summary, PGS research in Australia is well underway in a variety of aspects of PGS and research groups across Australia are making significant contributions to expanding the PGS evidence base. The implementation challenges identified internationally are also valid here and need to be investigated and managed in the Australian health system context.

National consultation

Themes derived from the national consultation data demonstrate the wide variety of PGS research needed to inform implementation:

- The value of PGS must be demonstrated: How do PGS add value for patients and populations above existing risk estimates? Cost effectiveness/benefit?
- Clinical utility: The utility for PGS in specific clinical contexts needs to be demonstrated (e.g., impacts on health behaviour); how/who decides on criteria for utility/who regulates?
- Infrastructure needs: Across the pipeline, from laboratory to the patient: needs are to be defined and evidence collected to guide provision of supporting infrastructure.
- Ethical and legal implications: These include data storage requirements and privacy, insurance implications, equity of access across groups in the community.
- Understanding and education: Professional and public; risk communication and perception.

The following considerations for PGS research were strongly supported by the consultation:

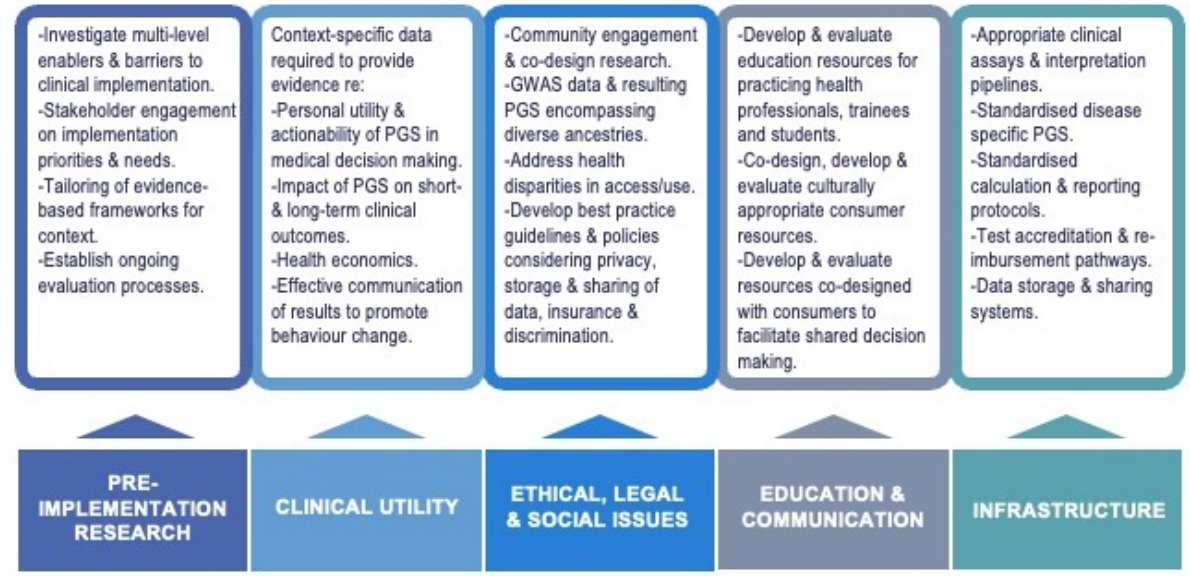
- Collaborative and multi-disciplinary research to prevent duplication of effort and to facilitate effective research translation, such as PGS research consortia according to disease or PGS application.

- Research should cover the PGS pipeline, from GWAS to health outcomes and health economics – specific areas of research can't be prioritised over others.
- As for any medical research, equity needs to guide all research and implementation, both from the perspective of PGS that apply equally across diverse ancestries and equity of access to PGS in healthcare.
- Scalability of demonstration projects important to facilitate timely implementation, noting that some diseases are further along the path to having the evidence base for clinical use.

Research gaps

Studies demonstrating clinical utility of PGS in specific clinical contexts appear to be the most underdeveloped area of research, but there are gaps across the spectrum of implementation, as summarised in the figure below.

Steps to implementation of PGS into public health and clinical care*



* We acknowledge the HGSA PGS working group for use of this figure.

Recommendations for PGS research in Australia

The following recommendations for PGS research in Australia are based on the data from landscape analyses and the national consultation. Each of the research streams are considered necessary for providing robust evidence to inform the implementation of PGS into the Australian health system. and not weighted according to importance. The landscape analysis and expert consultation **strongly underline the need for research to be multi-disciplinary and conducted across streams.**

Streams of research

Stream 1: PGS assay and test development	Stream 2: Evaluation and implementation of PGS	Stream 3: Education, understanding, workforce issues
• Assays and tests, linked with purpose/context • Regulation of PGS tests – robust, effective, clinical assays and interpretation pipelines; Includes process for regulation around updating of PGS assays based on new SNPs/evidence • Consistent reporting (standards) of PGS results: from lab to clinician, from clinician to patient. This includes developing systems to record PGS data and metadata to facilitate transparent trace-back to track SNP weights used in any stored PGS	• Development of PGS clinical tools or integration of PGS into existing risk tools • Implementation of PGS clinical tools in practice: - Population level implementation studies, e.g., into existing screening programs - Primary care implementation - Specialist services • Frameworks tailored to facilitate evaluation of validity and utility of PGS • Evaluation at every point along PGS pipeline from laboratory to patient health outcomes • Health economic evaluation at every stage, from informing PGS implementation protocols (e.g., using discrete choice experiments) to cost-benefit analysis to inform governments/health systems and identify impact on budgets • Intervention and behaviour change studies, including long-term health outcome/behavioural follow-up studies • Health system requirements associated with PGS implementation, including electronic health records, data storage, data ownership and access • Health technology assessment • Possible funding strategies for PGS implementation	• Education of clinicians and community education/health promotion • Social and ethical norms, such as community acceptance of PGS (e.g., is PGS seen as different to other non-genetic risk information?) • Insurance implications • Decision-making arising from a PGS result (e.g., preparedness to forego screening based on low-risk PGS) • Practitioner roles for conducting and reporting PGS tests (point of care: genetics health professionals, other specialists, primary care clinicians, direct to consumer testing)

Guiding principles

PGS research should be guided by the principles of:

- **Value:** PGS implementation needs to add value to the health system, individual patients, and/or public health.
- **Context:** Applications of PGS are context dependent and some contexts are further along the path to implementation.
- **Equity:** 1) Australian genomic reference data needs to represent the diverse genetic ancestry of the population; 2) equity of access to PGS for disadvantaged groups should be a consideration for implementation (as for any new healthcare intervention).
- **Collaboration:** Research must promote/demonstrate collaboration between researchers, clinicians, public health, and the community at all steps of the process and across disciplines.

Possible structures to support PGS research and implementation

A key theme of this project is that sharing of information/data sets across research groups in Australia and internationally will facilitate the optimal use of resources and minimise duplication. Consortia will be key to advancing translation into clinical practice.

A potential model would be the formation of an Australian Common Disease Genomics Alliance with a focus on PGS implementation, comprising experts in multiple disciplines. A consortium of this type would not aim to determine or direct the field but act as an identifiable forum for aggregating and exchanging expertise, advice and the development of collaborations, as well as a body to coordinate the sharing of data. **Australian Genomics**, as the national organisation for supporting the translation of genomics research into practice, could facilitate such an alliance with dedicated funding.

2. AIM, OBJECTIVES AND SCOPE OF THE PROJECT

In response to the Genomic Health Futures Mission (GHFM) Scientific Strategy Committee recommendations (2019) as to the design, delivery and priorities of the GHFM, the incubator project model was proposed. Genomics incubator projects aim to develop genomic health research priority areas considered to be of strategic importance to Australia, but which are not ready for large-scale funding, or where there is a risk of a fragmented collection of submissions to an open competitive call. Genomics projects (funded by MRFF) will be in areas considered time-critical to advance Australian genomic research strategy and clinical translation. Australian genomics incubator projects are tasked to form a national strategy group of experts and identify mechanisms for enhancing, maturing and advancing genomic research to drive clinical translation.

2.1 Aim and scope

The aim of this *Australian Genomics Polygenic Score Incubator Project* is to provide recommendations to the Australian Government Medical Research Futures Fund (MRFF) about research priorities to support polygenic score (PGS) implementation in the Australian health context.

The identification of PGS and their potential to improve human health is a relatively new area of research and only beginning to be implemented into clinical or public health practice. This report describes the current state of PGS research and applications in clinical and public health practice in Australia and internationally. The focus of the report is research that can inform implementation, but this does not diminish the importance of the ongoing and prolific scientific research to identify and validate polygenic risk alleles and develop improved PGS. Many studies and reviews document the state of GWAS and the algorithms for calculating and validating a PGS (e.g., Buniello et al, 2019 (1); Visscher et al, 2017 (2); Chatterjee et al, 2016 (3)), but they are not reviewed in detail here. Rather, the objectives of this report are to identify best practice in Australia and internationally and gaps in knowledge for implementing PGS in public health and clinical practice. Importantly, the report describes the types of evidence necessary to incorporate PGS into the Australian healthcare system with the appropriate safeguards and regulation. This will inform the focus and direction of research funded by the Australian MRFF to ensure it will contribute to the responsible, fair, clinically useful, and cost-effective implementation of PGS into Australian healthcare.

Trait versus disease: This project does not examine PGS associations with traits such as intelligence, height, or sporting ability, which have broader implications than health. Here we report on PGS only as they pertain to disease and disease risk factors.

A note on terminology: Throughout this report, we use the term polygenic score (PGS) rather than polygenic risk score (PRS) to reflect the fact that PGS may be used for disease diagnosis or therapeutic decisions as well as disease risk prediction. However, where PRS is part of a study title, PRS is used.

2.2 Objectives

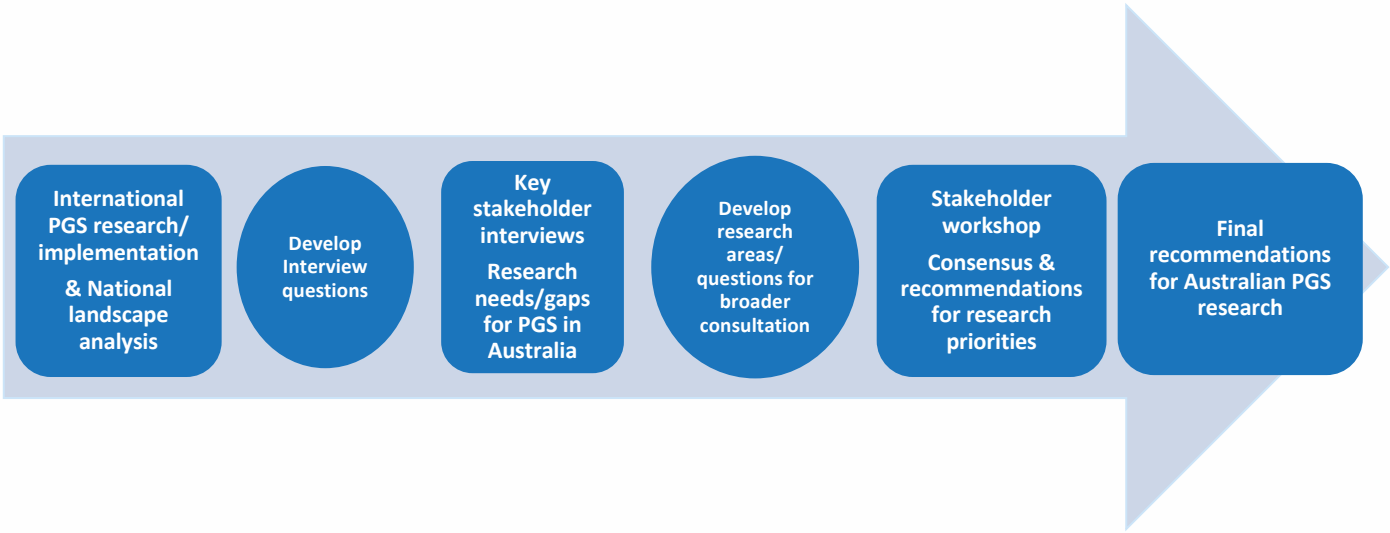
The objectives of the project are to:

- Investigate international best practice, approaches, and health system integration
- Undertake a national landscape analysis of existing research activity in the area
- Undertake a national consultation to elicit the views of key people with an interest/expertise in PGS
- Use the above data to make recommendations to inform future PGS research and implementation for Australia.

2.3 Project process and oversight

In line with the aim and objectives, the stages of the project are outlined below, with designated responsibilities for the Project Strategy Group and the Project Working Group as follows:

- The Project Strategy Group provided expert oversight of the entire project, including developing the methodological approach, providing advice at each stage of the process, and approving the final recommendations for Australian PGS research.
- The Project Working Group conducted the research, analysed the data from the national consultation (interviews and stakeholder workshop), drafted the recommendations, and prepared the report.



3. PROJECT TEAM

3.1 Project Leads

- Professor Andrew Wilson, Director, Menzies Centre for Health Policy and Economics, University of Sydney; Chair, Pharmaceutical Benefits Advisory Committee.
- Mary-Anne Young, Head, Kinghorn Centre for Clinical Genomics & Clinical Translation & Engagement Platform, Garvan Institute of Medical Research; Conjoint Senior Lecturer UNSW, Sydney.

3.2 Project Strategy Group

- Andrew Wilson and Mary-Anne Young (Co-chairs).
- Professor Anne Cust, Professor of Cancer Epidemiology, Deputy Director of the Daffodil Centre (The University of Sydney, a joint venture with Cancer Council NSW).
- Professor Jon Emery, Herman Professor of Primary Care Cancer Research, University of Melbourne, and Primary Care Research and Education Lead, Victorian Comprehensive Cancer Centre; Visiting Research Fellow, Department of Public Health and Primary Care, University of Cambridge.
- Dr James Harraway, Genetic Pathologist, Sullivan Nicolaides Pathology, Queensland.
- Professor Paul James, Consultant Clinical Geneticist, Director Parkville Familial Cancer Centre and Group Leader of familial cancer research, Peter MacCallum Cancer Centre, Melbourne.
- Professor Naomi Wray, Statistical Geneticist, NHMRC Leadership Fellow, Institute for Molecular Bioscience (IMB) and the Queensland Brain Institute (QBI), University of Queensland.

3.3 Project Working Group

- Mary-Anne Young, Project Co-lead
- Dr Stephen Hughes, Project Coordinator, University of Sydney
- Amali Disanayaka, Research Support/Coordinator, Australian Genomics
- Dr Veronica Collins, Project Officer.

4. DEFINITIONS & ABBREVIATIONS

4.1 Definitions

The following definitions are those adopted for the purposes of this report, acknowledging that other definitions may be appropriate in other contexts.

Allele	One of two or more versions of a DNA sequence (a single base or a segment of bases) at a given location in the genome.
Clinical utility	Definitions vary depending on the clinical context in which the test is being used. In clinical genetics, clinical utility refers to the effect of genetic testing information on diagnosis, prognosis, therapeutic management, the health and psychological well-being of patients and their relatives, and healthcare system costs. It is closely linked to personal utility.
Clinical validity	A measure of how well the test performs in a clinical setting. Often described in terms of ability to predict a clinical condition, including sensitivity, specificity, and positive and negative predictive values.
Genome-wide association study (GWAS)	An approach where large numbers of common genomic variants (single nucleotide polymorphisms, SNPs) are compared between individuals who have a particular condition (cases) and those without the condition (controls), to identify the SNPs that are associated with the condition.
Health technology assessment (HTA)	A multidisciplinary field that addresses the health impacts of health technology, considering its specific healthcare context as well as available alternatives. Contextual factors addressed by HTA include economic, organisational, social, and ethical impacts. HTAs inform policy decision-making in healthcare.
Heritability	The proportion of variation between individuals in a population for a given trait or disease that can be attributed to genetic variation.
Integrated risk score or model (also known as a combined risk score or model)	A risk score that combines PGS information with other risk factors such as age, sex, clinical measures, environmental/behavioural risk factors and other biomarkers, in which the weights allocated to each risk factor are known (have been estimated previously) and can be applied to the measures of the risk factors in an individual with unknown future disease status.
Personal utility	There are several definitions, depending on context. Personal utility can be defined as the value of the test information to the person being tested. It is closely linked to clinical utility but does not necessarily involve a specific health outcome.
Polygenic score(s) (PGS)	Also called polygenic risk score (PRS) or genetic or genomic score: a single value, calculated by aggregating the number of disease or trait alleles carried by an individual, weighted by the effect size derived from the discovery GWAS and standardised to a representative population distribution. This single value quantifies an individual's estimated genetic liability to a disease or a trait.

Precision medicine	An approach that uses uniquely personal information (including genes, environment and lifestyle) about an individual to help guide health-related decisions. Precision medicine implies a stratified approach to medicine based on person-specific data but does not imply person-specific approaches to health (known as personalised medicine).
Single nucleotide polymorphism (SNP)	A DNA sequence nucleotide (adenine, thymine, cytosine, or guanine) at a given genomic location that varies between people in a population. SNPs with two alternative nucleotides are studied, commonly limited to those with the minor allele frequency > 1%.

4.2 Abbreviations

CAD	Coronary artery disease (also known as coronary heart disease or CHD)
CVD	Cardiovascular disease
DTC	Direct-to-consumer (testing)
EU	European Union
GWAS	Genome-wide association study(ies)
HTA	Health technology assessment
IVD	in vitro diagnostic medical device
MSAC	Medical Services Advisory Committee (Australian Government)
MRFF	Medical Research Futures Fund
NATA	National Association of Testing Authorities
NHGRI	National Human Genome Research Institute (USA)
NHMRC	National Health and Medical Research Council (Australia)
NHS	National Health Service (UK)
NIH	National Institutes of Health (USA)
PGS	Polygenic score(s)
PRS	Polygenic risk score(s)
RCT	Randomised controlled trial
SCoS	Standing Committee on Screening (Australian Government)
SNP	Single nucleotide polymorphism
TGA	Therapeutic Goods Administration (Australia)
UK	United Kingdom
USA (or US)	United States of America

5. BACKGROUND

The application of genomic technologies in health is expanding, including a greater understanding of the genetic contribution to common complex diseases, such as heart disease, diabetes and cancers (4). Complex diseases are named as such to reflect their complex aetiology comprising both genetic and non-genetic (behavioural and environmental) risk factors acting together. The increased availability of faster and cheaper technologies to study the genetic contribution to disease at a population level has facilitated a proliferation of genome-wide association studies (GWAS), which have led to identification of common genetic variants associated with complex diseases (2). Associations with disease are determined by comparing the frequency of genetic variants between GWAS study participants known to have a particular disease (cases) to those without the disease (controls), conducted across the genome. Mostly, associations with single nucleotide polymorphisms (SNPs) are reported, but other common genetic variants (such as insertions/deletions) can be studied. While individually each SNP may have a minimal impact on disease risk, their combined effect (known as a polygenic score) is associated with variation in risk of disease.

5.1 What is a polygenic score?

A polygenic score (PGS, also called polygenic risk score or PRS) is a single aggregate score calculated as the count of SNP risk alleles carried by an individual weighted by an effect size derived from a GWAS (5, 6). PGS are validated by applying them to a cohort with known disease status to determine the strength of association with the disease of interest. A PGS can then be applied to an individual to determine their future risk of developing a disease by comparing their score to the distribution of scores from the reference population. PGS can also be used to inform prognosis and therapeutics if appropriate GWAS are available to generate SNP weights (currently few such GWAS exist).

The optimal choice of variants to include in a PGS and the weights given to each variant is an active area of research (2, 3, 6), which has implications for regulation of PGS tests (see 6.1). Developing PGS for a range of clinical contexts is a rapidly developing field and there can be a variety of algorithms indicating risk for a particular disease. Recognising that PGS are estimates of the genetic contribution to disease risk, PGS will improve over time, because of both larger GWAS generating more accurate weights for SNPs in the PGS and better statistical methods. Hence PGS will change over time, and this needs to be managed when used in clinical practice.

Complex disorders are only partly due to genetic factors, with non-genetic factors also playing a large role. Hence, PGS are expected to be combined with risk estimates of other contributing factors to make an integrated risk score (6).

How will polygenic risk be communicated?

There are three main options for representing the risk information from a PGS: as a percentile within a given population (e.g., a PGS at the 95th percentile); as a relative risk or odds ratio (e.g., a 2-fold risk for people in the top 10% of a PGS distribution compared to the remaining 90% of the PGS distribution); or as an absolute risk (e.g., a percentage 10-year risk for developing a condition) (7). It

is not clear which form of risk representation will be most suitable for PGS in practice and it is likely to depend on the clinical context and the target group. It will also be important to convey the uncertainly around the PGS risk estimate and to be able to link the risk to a clinical action by determining a threshold for action; for example, the risk level above which it is appropriate to prescribe a statin or offer screening (7).

The difference between PGS and other risk factors

Although similar in many ways to other environmental and biomarker risk factors used in clinical practice, a PGS has some unique features to consider when planning for widespread implementation:

- A PGS is constant throughout life. It can be used very early in life to predict risk and is not dependent on the stage of life at which it is measured. However, disease risk will change over the life course depending on the effects of environmental and behavioural factors.
- A PGS can be used to distinguish risk within families, where there is an overall familial risk for a condition.
- For many conditions, the utility of a PGS will be greatest when it is combined with traditional non-genetic risk factors but these combined risk models involving PGS require validation.
- A PGS may tell us something about causality of a condition in contrast to most biomarkers.

What makes a good PGS?

The qualities that define a good PGS are not dissimilar to those for other assays used in public health or clinical practice. A PGS needs to have an acceptable level of accuracy, be reproducible, be transferable across environments and populations, and be easy to calculate so that non-genetic specialists have the knowledge and tools for implementation. There are currently challenges with PGS across all these domains.

Prediction accuracy: Accuracy is dependent on the genetic contribution to the disease or trait and the sample size of the GWAS studies that provide estimates of SNP effects. Although there will always be uncertainty around a PGS, just as for any other disease risk factor, it needs to be demonstrated that the PGS can provide a certain level of accuracy so that it consistently contributes information over and above that gained from existing risk factors. As more and larger GWAS are conducted, the accuracy will improve. For some conditions, including breast and prostate cancers and type 1 diabetes, the accuracy of PGS in European populations is already at least as good as other clinical predictors (8). However, no matter how many SNPs are included in a PGS or how good the statistical methods, the accuracy of PGS in predicting disease onset will always be limited by the genetic contribution (i.e., heritability) of the condition in question and so non-genetic risk factors will need to be considered in risk prediction for diseases and traits that are not highly heritable (6).

Transferability: PGS are currently not very transferable across populations with different ancestries. It has been reported that over 85% of participants in GWAS studies have European ancestries (and 72% of participants from the USA, UK and Iceland), with less than 9% having Asian and less than 1% African ancestries, although initiatives are now leading to more studies in African and Asian

populations (9). This bias is typical of medical research, but genetic studies allow direct investigation of the effect of ancestry on test accuracy. Currently, PGS have lower accuracy in non-European-ancestry populations (8). However, accuracy can be improved by increasing both European and non-European ancestries in GWAS (with open data sharing standards needed for all ancestries and for genetic studies of all sample sizes) (8), as well as the development of statistical models that optimise PGS in non-European populations (10).

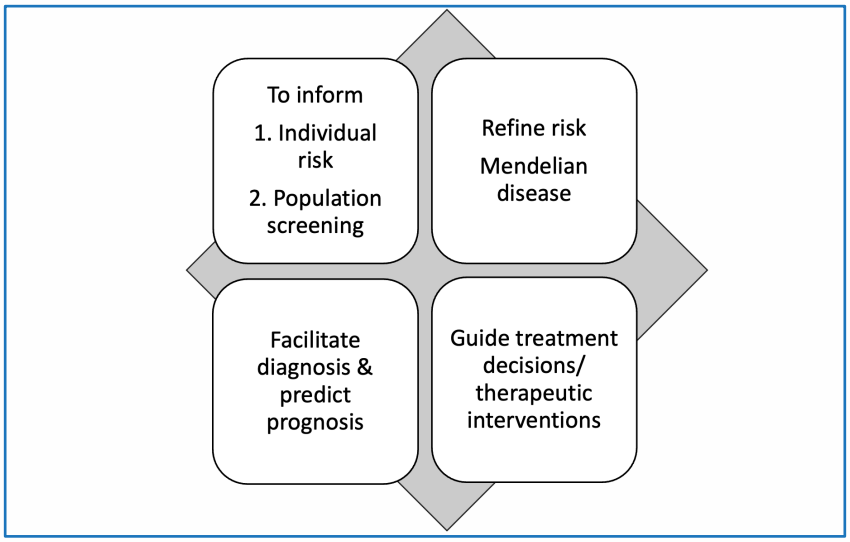
Easy to interpret: There is a need for health professionals who may not be expert in PGS methods to be able to understand PGS and interpret them for patients.

Reproducibility: Currently different models (statistical methods and/or GWAS data) can lead to a different PGS for the same health condition, such that more work is needed to determine the best models to give reproducible PGS within a particular clinical context. Initiatives such as the Polygenic Score Catalog aim to support reproducibility by acting as a central store of data on PGS that allows others to have access to the necessary information to be able to reproduce a PGS and apply it in the clinical setting (11). Ideally, all researchers developing PGS will share all the necessary data according to agreed reporting standards to facilitate reproducibility (11).

5.2 Potential uses of PGS

There is a breadth of possible applications of a PGS in both public health and clinical care (12-14), as depicted in Figure 1.

Figure 1: Possible healthcare areas for PGS use



PGS are potentially useful (in some cases already in use), to:

- inform population screening and provide personalised risk estimation for screening or preventive treatments/interventions (also in combination with environmental and biomarker risk factors)
- aid in disease diagnosis (e.g., to distinguish between type 2 diabetes and late-onset type 1 diabetes)

- provide information that can modify risk for a person carrying a pathogenic genetic variant associated with a high risk of disease (referred to as a Mendelian disorder).
- help with treatment decisions/pathways (e.g., to inform use of statin therapy for individuals at high risk of CAD or hormone treatment in those at high risk of breast cancer) and guide therapeutic interventions (the use of PGS in pharmacogenomics is not yet well developed but is under investigation (15, 16) and, in general, much larger GWAS are needed to generate PGS in this context).

However, there is much discussion around the need to demonstrate the "value" of PGS (see Box 1) before widespread implementation, which can only be properly assessed when there is a clearly defined clinical purpose and context for use (see Box 2) (12, 17-19).

Defining purpose and context can influence the thresholds that are deemed acceptable for the test to be clinically useful and the clinical outcomes, such as interventions or risk behaviours, that may be influenced by the information from a PGS (17). In many situations the value is relative to existing approaches; how much additional benefit is gained in decision making from the inclusion of PGS? In addition to demonstrating the value of a PGS, other factors such as competing priorities, infrastructure requirements, opportunity costs and resources will feed into decisions around PGS implementation.

Box 1: What is meant by the value of a PGS test?

Value can have different meanings depending on the person using the term, the purpose and context in which it is being used, and who is benefiting from the test. The value of a PGS test (as for other health tests) can be assessed by its validity and utility, including:

- Analytic and clinical validity: does the test do what it purports to do consistently and with acceptable variability? Are sensitivity, specificity and positive predictive value acceptable?
- Clinical utility: A broad term relating to the judgement of the value or usefulness of a test in clinical contexts, such as population health and screening. May include patient health outcomes (including physical and psychological; individual or population-level), clinical decision-making (e.g., does it help a health professional and/or an individual make informed decisions about care options?) or clinical workflow (e.g., does it provide faster test results, is it more cost-effective than existing tests?). Potential harms (such as misclassification, misunderstanding of PGS information, psychological effects) also need to be assessed along with an evaluation of the benefits versus the harms.
- Personal utility: Closely linked to clinical utility and subjective in nature, such as a person's reason for having a test and the effect of the test on that person; those benefits or harms that are primarily outside of clinical contexts and can encompass 'information for information's sake' (particularly applicable to genomic information accessed outside the health system).

Value also incorporates economic value as defined by cost-effectiveness or cost-benefit, which may be considered as part of clinical utility in its broader definition.

Box 2: What is meant by context for a PGS test?

Context refers to the specific area of use of the PGS and/or the health condition to which it applies. Potential uses of PGS include:

- Disease risk prediction in healthy individuals or for early detection (screening) or prevention
- Diagnosis refinement
- Prediction of disease progression and recurrence
- Informing population screening programs – to determine who should be screened, the mode of screening to be used, or to guide and encourage the uptake of preventive behaviours/medications
- Therapeutic options for those diagnosed with a condition where suitable GWAS datasets are available (currently there are few).

The possible uses of PGS will differ depending on the health condition under investigation and whether it is for an apparently healthy individual or an individual with a specific health condition or at familial risk of a condition. The use of PGS in some health conditions presently have a greater evidence base and are better candidates for earlier implementation into healthcare (see section 7.1)

Given the burden that common, complex diseases place on the health system, the use of PGS to identify high-risk subgroups of the population is emerging as a research priority area, with large funding investment internationally. However, given their recency, common disease genetic risk predictions have rarely been carried through to health system implementation, and there remains the challenge of incorporating environmental (e.g., socioeconomic factors, access to care, health behaviours) and other biomarkers (e.g., cholesterol, blood pressure for heart disease risk) in health risk prediction. Further, as for any biomarker, there is a need for PGS to be applicable across ancestral backgrounds, and to be accessible to all in the community, regardless of socioeconomic status or level of education, to deliver potential benefits equitably.

5.3 Current status of PGS in Australia

In Australia, PGS is not part of routine clinical practice, but it is available through commercial companies. To access testing from these companies, tests must be ordered by a medical practitioner rather than by the consumer directly (https://genetype.com/). Alternatively, consumers can access testing through overseas private direct-to-consumer (DTC) laboratories. Unfortunately, accessing PGS in this way means that often the supports around receiving test results are missing, such as interpreting the meaning of test results for an individual patient, health professional understanding of the result if the patient seeks help, and indications for intervention if any. PGS testing is also being done in research settings with varying levels of participant feedback of results.

Given the availability of PGS in the private domain and the rapidly burgeoning field of PGS research, the challenge for Australia, as for all countries, is to gather the evidence to guide incorporation of PGS into public health and clinical practice in an informed, safe and ethical way, taking into account the particular characteristics of the Australian healthcare system.

6. CHALLENGES FOR PGS IMPLEMENTATION

The use of PGS in public health and clinical practice is currently in its infancy and there is still much to be learned before PGS implementation into health care in a responsible, ethical and cost-effective manner.

Apart from the lack of a gold standard for analysis affecting the analytic validity of a PGS (see *What makes a good PGS?*, above), there are other challenges to address before widespread clinical translation (8, 12, 13, 17, 18, 20). These include:

- Test methodology: Developing test evaluation frameworks for PGS to provide evaluators with a consistent methodology for evaluation of PGS, from the laboratory test to clinical use
- Regulation: Determining the appropriate regulatory oversight to ensure the PGS is safe and effective in the clinical contexts in which it will be used and to prevent non-ethical use
- Demonstrating the clinical utility of PGS
- Developing best practice guidelines
- Developing appropriate evidence-based education for health professionals and the public
- Ensuring that health disparities are not exacerbated by inequitable access to PGS tests
- Identifying funding sources for various PGS clinical and population health applications.

6.1 Evaluation and regulation of PGS tests

Test evaluation

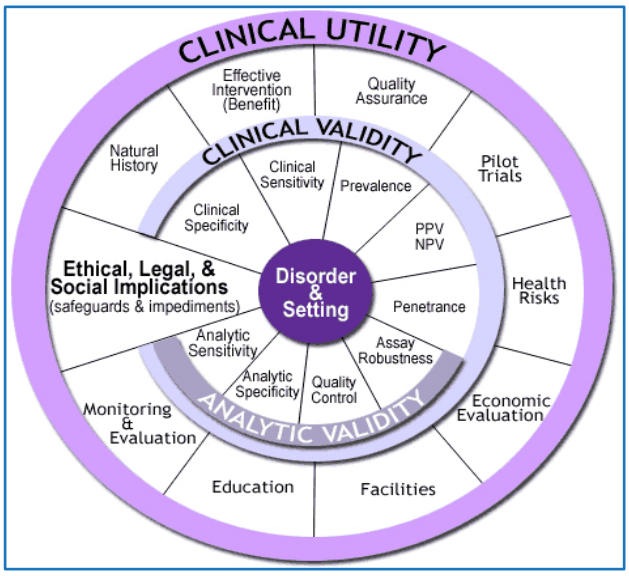
Many working in the PGS field regard PGS tests as not intrinsically different to any other biomarker (6), but there is likely to be community misunderstanding of the power of genomic information that may lead to unrealistic expectations of the predictive ability of PGS (18). On the other hand, there are concerns about whether there is added value from a PGS for clinical decision making and risk prediction in complex diseases, over current risk tools (18).

It is important that PGS tests are evaluated to determine their usefulness in a variety of clinical contexts, for both population and individual patient health outcomes. Until recently, most research has focused on developing PGS models or combined risk models and assessing their predictive ability for a particular condition, that is, analytic and clinical validity studies (17). It is also necessary to incorporate a PGS risk model into a clinical risk assessment tool for use in practice and to assess its impact on healthcare pathways (18). Defining the clinical utility of a PGS test is not straightforward (particularly in the time frame of standard trials). It requires clear definitions of the purpose of the test and the clinical context in which the test will be used, including the target population and the health interventions and outcomes arising from the test (specific use cases). This will determine the required evidence base and the thresholds that need to be met for the test (18). Moreover, some PGS tests may be considered to have personal utility but not clinical utility (18), such as providing information on risk of developing Alzheimer's disease in the absence of proven effective interventions.

Test evaluation frameworks are designed to define the evidence required for implementation of clinical tests and to understand the various aspects of test performance, including clinical utility (18).

A number of frameworks have been proposed for evaluating genetic/genomic tests, with many based on the ACCE (**A**nalytic validity, **Cl**inical validity, **Cl**inical utility, **E**thical, legal, and social implications) model (21), developed by the CDC (USA) Office of Public Health Genomics (Figure 2).

Figure 2: The ACCE Model for evaluating genetic tests*



* Available at: https://www.cdc.gov/genomics/gtesting/acce/index.htm (2010)

PPV: positive predictive value NPV: negative predictive value

Although the ACCE model has been used extensively and may be appropriate for evaluating PGS tests, some have argued for a broader framework for evaluating genomic tests that combines aspects of the ACCE model with a health technology assessment (HTA) approach (18, 21). HTA evaluation frameworks include the economic and organisational aspects of the delivery of the testing program, which may be particularly relevant for universal healthcare systems (21). There may also be some aspects of a genetic test evaluation framework that are not as relevant to PGS tests as they are to genetic tests for rare high penetrance variants associated with much higher disease risk. Evaluation frameworks from outside of genetics may also be relevant to PGS evaluation.

Having an agreed framework for evaluating PGS tests with a common methodology that can be adapted for each individual test and health system (21) will not only serve to systematically evaluate each PGS test in its clinical context, but can help to define the gaps in evidence required before clinical implementation (18).

Population based screening principles

Screening programs in Australia must satisfy criteria outlined in the Australian Government Department of Health *Population Based Screening Framework*, which is based on the Wilson and Junger (WHO, 1968) screening principles (22). The 2018 update has a section on genomic screening and states: “A key emerging issue is the potential of genomic testing, technologies and knowledge to affect screening”. The Standing Committee on Screening continues (SCoS) to keep a watching brief on the use of genetic and genomic technologies and their potential for application in screening at

the population level. The SCoS continues to liaise with other Australian Government committees currently considering genetic and genomic issues.

Additional guidelines may also need to be considered to enable PGS to be used in population screening; for example, for PGS to be used in a newborn screening program, the screening program needs to follow the guidelines of the *Australian Newborn Bloodspot Screening National Policy Framework* (23).

Regulatory approval

Regulation is necessary to ensure safety, efficacy and effectiveness of medical tests and may apply at multiple levels (17, 18). For PGS, the regulatory landscape will be complex and may need to consider each level of PGS development, from the risk model to the combined risk tool, to the test to be used in a specific population for a specific purpose (18). The evidence needed for regulatory approval may not be as extensive as that required by those making decisions about PGS implementation into healthcare, where clinical utility may need to be more rigorously demonstrated (18.).

In Australia, implementation of PGS into healthcare will require changes in Australia's health and medical regulatory framework. As PGS move from research into healthcare, complex relationships between stakeholders including diagnostics, research laboratories, the direct-to-consumer industry, biobanks, clinical services, private and public healthcare, public-private partnerships, the biotech industry, and others, will need to be managed.

The National Association of Testing Authorities (NATA) is the Australian laboratory accreditation body recognised nationally and internationally. NATA assesses organisations against international standards for laboratories and provides accreditation for technical competence and clinical oversight of tests used for decision-making (in vitro diagnostic medical devices; IVDs). IVDs are regulated by the Therapeutic Goods Administration of Australia (TGA). NATA and the TGA will play a key role in accreditation and regulation of PGS tests intended for clinical use.

Public funding of PGS in Australia will require HTA, whether PGS are made available through public institutions or private laboratories. The most likely pathway for such assessment would be the Medical Services Advisory Committee (MSAC) of the Australian Government[1]. MSAC provides advice to the Federal Health Minister on whether there should be Medical Benefits Schedule subsidy for diagnostic tests (or under the National Health Reform Agreement shared funding with the states and territories). In doing so it must consider the need for the technology, the need for public subsidy and the cost-effectiveness of the test, intervention, or service.

Applications to MSAC must follow the guidelines for submissions for funding[2]. MSAC has considered many applications for panel and single gene testing but has yet to consider any applications for PGS. It has considered risk scores incorporating genetic information for predicting response to treatment,

[1] See: http://www.msac.gov.au/internet/msac/publishing.nsf/Content/factsheet-06

[2] See: http://www.msac.gov.au/internet/msac/publishing.nsf/Content/E0D4E4EDDE91EAC8CA2586E0007AFC75/$File/MSAC%20Guidelines-complete-16-FINAL(18May21).pdf

for example in breast cancer[3], and there are many similarities with the more general issues that arise for PGS.

With the rapidly changing PGS landscape, regulatory bodies will need mechanisms to incorporate new knowledge in a flexible and timely fashion.

6.2 Ethical, legal and social issues (ELSI)

Diversity and equity

There are two areas where the development and implementation of PGS have potential to widen existing health disparities: (i) lack of inclusion of diverse populations in GWAS and (ii) lower access to and uptake of PGS amongst disadvantaged groups. These issues are widely known and discussed in many commentaries (8, 12-14, 24-28).

The issue of lack of diversity in studies is relevant to any biomarker used in medicine; however, the ability to directly measure genetic differences between ancestries forefronts this issue. With heightened awareness of the problem, there are now deliberate strategies to include more diverse ancestries in GWAS studies, as described in the section above (Transferability of PGS models), and studies are currently underway (for example, the *All of Us* study (29); the *East London Genes and Health study* (30); the Aotearoa Variome Project[4]; and work led by Daniel MacArthur in Australia (see Section 7.3)). Moreover, novel methods which improve the predictive accuracy of PGS by combining information derived from studies across ancestries as well as within ancestries are being developed (8, 10, 19). It has been suggested that other demographic characteristics may also affect the predictive power of PGS, such as sex, age and socioeconomic status, and these factors may require further consideration in PGS studies (25).

As for other areas of healthcare, access to and uptake of PGS may be lower in more educationally and economically disadvantaged groups (8, 28). However, in contrast to some countries, particularly the USA, Australia has the advantage of a universal public health system. If implemented into public healthcare, PGS will theoretically be available to all Australians, subject to the approved health indications and use cases. However, for equity of access to be realised, public funding is essential and public education will be required for individuals to understand the possible benefits of PGS in their circumstances. Moreover, systems will need to be designed to reduce barriers for communities that often have lower use of health services. There is also a possibility when focusing on genomic testing, that less attention is given to the social determinants of health, which are still the biggest drivers of health and disease (24).

The current evidence suggests the diversity and equity challenges are not insurmountable, are being addressed, and should not stop the field from progressing. However, equity needs to be front and centre of implementation research and planning.

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[3] See http://www.msac.gov.au/internet/msac/publishing.nsf/Content/F110B75361D91B5DCA2583CF00166434/$File/1342.5%20-%20Final%20PSD.pdf

[4] See: https://www.genomics-aotearoa.org.nz/our-work/health-projects/aotearoa-nz-genomic-variome

Potential for harm from PGS test results

Misclassification

PGS provide an estimate of risk and so the concept of misclassification is different to that associated with diagnostic genetic tests used for Mendelian disorders. Therefore, the issues around misclassification based on a PGS are not dissimilar to those for other risk screening tests. However, when introducing a new test, it should be demonstrated that the potential for misclassification is minimised given the specified threshold for action (threshold will depend on the purpose and context of the test). With respect to HTA and PGS, the most important context for misclassification is where a patient is denied a treatment which might be beneficial or given a treatment when it is not necessary. This is almost inevitable when the score is continuous, and a threshold is applied above or below which a clinically important decision is made. In setting the threshold there is usually a trade-off between these two outcomes. For example, if a PGS is used to guide frequency of cancer screening, then some patients with a low-risk PGS allocated to low intensity screening will develop cancer – what is the trade-off between better detection in those at high risk screened more intensely compared with the miss rate in the lower intensity screening population? Similarly, if there is a treatment that has significant levels of adverse events that it should be avoided, if possible, then a PGS that predicts response will need to be weighted towards not missing a benefit of treatment. Another consideration is that PGS may improve over time (based on larger GWAS and improved statistical methods). Necessarily, the revised PGS will result in some changes in allocation (both in and out) of individuals to the high-risk group. Careful communication to both clinicians and patients will be required to interpret these changes.

Reduction in screening for low-risk PGS

It is often proposed that one benefit of risk-stratified screening (for individuals and for cost-effectiveness) is the reduction in screening, either through later age of initiation or reduced frequency, for those with a low-risk PGS (14). Slunecka et al (5) have cautioned that we need robust data to support such a change in screening guidelines before putting it into effect, given the harm that may come from a missing or late diagnosis. They suggest that in the short term, PGS risk should only be used to enhance interventions for high-risk PGS (5). The level of evidence needed to change guidelines will be context dependent, such as the health cost of missing a diagnosis or conversely, over-treatment (as described in the previous section).

Genetic exceptionalism

Although PGS information can generally be considered like any other risk factor, genomic information may be viewed by individuals, health professionals or regulatory bodies as different to other health information, requiring special consideration (31). Whether genomic information such as PGS leads to a more fatalistic attitude to developing disease (or conversely, is likely to motivate preventive behaviours) is also not well understood (32). Education is key to public and health professionals' understanding of the limitations and uncertainty of PGS risk information, and the importance of considering PGS in the context of other non-genetic risk factors, along with how best to communicate PGS information (7). Many concerns raised about implementation of PGS, such as

transferability across ancestries are concerns valid for any biomarker. While such issues are important to address, we need to ensure the barrier for implementation of PGS is not inadvertently being set higher than for other biomarkers.

Life insurance

Up until now, concerns around the effect of genetic testing results on risk-rated insurance have related to testing for rare, pathogenic variants in monogenic conditions, in either clinical or research settings. The use of genetic test results to discriminate against people is defined as genetic discrimination (33). Genetic discrimination related to insurance is a concern around the world and in response, several countries have banned or restricted the use of genetic test results in insurance (34). In 2019, the Financial Services Council (the peak body that represents most Australian life insurers) introduced an industry self-regulated partial moratorium on the use of genetic test results, which research suggests has ongoing issues with protecting consumers (35). In a survey of health professionals (genetics specialists and others), many felt the moratorium is inadequate and most believe government oversight is necessary (36).

How PGS results might be treated by insurers in Australia is unknown, but insurance implications and protection for consumers need to be considered as part of implementation planning, in consultation with the insurance industry. The number of test results from PGS is likely to be far greater than current genetic tests and there is potential for misunderstanding of the meaning and predictive power of PGS.

Direct-to-consumer PGS

Several DTC genetic testing companies provide PGS tests for health conditions including type 2 diabetes, breast and other cancers, and CAD. The Australian company Genetic Technologies (now Genetype) has a US partnership to commercialise a suite of polygenic risk tests, which are available to order online (https://genetype.com/). As described earlier, medical professionals can order PGS tests or individuals may access tests directly through overseas providers on a user-pays basis, which have varying levels of support for returning results and interpretation of the test. Some individuals may take their DTC result to their doctor for help with interpretation (37), which can be challenging for the medical professional.

There are many potential problems with DTC PGS tests: lack of accreditation and regulation; lack of supporting information and counselling; data privacy; limitations of tests not communicated to consumers; tests from different companies may return a different result; and some tests are provided only to people of European ancestries. Recommendations for how Australia might be more proactive in education and regulation of DTC genetic tests to protect consumers have been proposed (27); however, the role of DTC testing in the future, when PGS is available in the Australian public healthcare system remains to be seen.

6.3 Health system integration

Data and health information challenges

Comprehensive strategies for compiling, storing and retrieving health information are necessary to integrate PGS into routine clinical care. To ensure future utility of stored genomic information, consideration needs to be given to how it is stored. Storage of genomic information is complex and the optimal way to store genomic information used in clinical and research genomics more broadly is not yet clear. PGS will continue to evolve as more evidence is accumulated about the associations between specific SNPs and disease risk, prognosis and response to therapy. While an individual's genetic profile will not change, if testing is confined to test-specific SNPs, then retesting will be required as algorithms add new genomic markers. If, however, initial analysis is genome wide, then recalculation of risk requires access to that data. Overall, it may be preferable to see storage of such genetic information in a way that allows a patient (and thereby clinician) access anywhere at any time. This could occur through centralised storage approaches (e.g., MyHealthRecord) through connected electronic health records, as is occurring in many state and territory health systems (medical records held locally or regionally but with common patient identifier across all records), or through a patient-held record.

Australian Genomics (for the Australian Government Department of Health) is developing *Preliminary implementation recommendations for a national approach to genomic information management*[5], which are presently out for consultation by interested parties.

Workforce readiness (education) and public acceptance

Professional readiness

The National Health Genomics Policy Framework[6] states: "the integration of genomics into health care is highly dependent on the development and expansion of an appropriately literate, skilled and resourced workforce". This is a significant challenge for all health professional disciplines, including general practice. The RACGP has developed the *Genomics in general practice resource (2018),* but this does not address PGS specifically (38).

Workforce readiness for PGS implementation, from data managers and technology designers to laboratory personnel who develop PGS reports for clinicians, to clinicians interpreting and communicating results to patients, has not yet received much attention (13). Health professional understanding of PGS information and communicating this risk information to patients is integral to clinical utility of PGS; for the benefits of PGS to be realised, there needs to be changes in health behaviours or treatments based on test results. The evidence for behaviour change is not strong so far, and risk communication is an important part of motivating behaviour change (7).

The application of PGS will go beyond the realm of specialist genetics clinics, with primary care physicians and other specialists likely to be involved. Leadership from the genetics community may

[5] See: https://www.australiangenomics.org.au/wp-content/uploads/2021/06/Preliminary-NAGIM-Report_1.04.2022.pdf
[6] See: https://www.health.gov.au/resources/collections/national-health-genomics-policy-framework

be useful in upscaling genetic counselling protocols to the broader clinical community, but education at all levels, from medical and other health professional training to continuing professional development, will need to be considered (5). Clinical practice guidelines and point-of-care resources will be essential (39).

Research on risk communication in other areas of genetics and healthcare can inform effective communication of PGS, and large PGS research studies, such as the eMERGE Network investigators and Our Future Health (see 7.2) may provide some guidance on optimal communication strategies (13). There are also smaller studies trialling communication strategies (e.g., a decision aid (40); a mobile phone app (41) and telephone-based genetic counselling (42)). The most effective mode of communication will also depend on clinical context, level of risk, and patient preferences.

Public understanding and acceptance of PGS

Public understanding of genetics and uptake of clinical genetics services is generally low (43), and it is not clear yet how PGS information will be understood by the public at large and patients with specific health conditions. Health promotion campaigns and broad educational strategies will be required, particularly if PGS is incorporated into population screening programs targeting healthy people. There is some evidence that PGS in specific clinical contexts is acceptable to patients and does not cause psychological distress; in fact, these small studies have shown patients value information arising from PGS (44-46).

Laboratories and funding

Currently, PGS are accessed either on a user-pays basis from commercial companies or as part of research studies and not through public health systems or on a large scale. The capacity of laboratories to provide the testing has therefore not yet been tested, and possible funding mechanisms are not clear. Cost-effectiveness studies will be required before any wide-scale implementation would be considered.

A UK analysis of the requirements for implementing a CVD risk score into the “NHS health check” notes that If genotyping were to be implemented at scale using current NHS genetics laboratories, it would have a detrimental impact on current service provision (47). The authors suggest an alternative could be for commercial providers to deliver genotyping services, including analysis, interpretation and reporting on a population-wide basis from blood or saliva samples (47). The costs of alternative models for laboratory services would need to be factored into health economic modelling.

See the section on Regulatory approval (above) for further discussion of public funding for PGS.

7. THE CURRENT LANDSCAPE OF PGS (AUSTRALIA AND INTERNATIONALLY)

The rapidly changing field of PGS research and implementation is evidenced by the ongoing publication of numerous studies, commentaries and expert opinion pieces in the academic literature and articles in the popular press. Research is happening in many countries, including Australia, with varying levels of funding commitments from government and private funders. As for many areas of medical research, particularly with respect to genomics, much of the work is undertaken in the United Kingdom (UK), the United States of America (USA or US), Europe and Australia, although there are attempts to make PGS a more inclusive enterprise with research in parts of the world with less developed economies.

Despite great interest in the potential of PGS to improve human health, implementation into clinical practice is still underdeveloped, except where clinicians and/or individuals access tests from private laboratories on a user-pays basis (see section 6.2). Therefore, agreed best practice approaches, clinical guidelines, and examples of successful health system integration are not yet available. However, designing supporting infrastructure, developing research collaborations and networks, and studies to show clinical utility are well underway to collect the evidence and support the implementation of PGS into clinical practice. It is generally agreed that PGS will become part of clinical practice in a variety of ways ("not if, but when"), so the current effort is on conducting the research and developing policies and safeguards to overcome the barriers and challenges outlined in section 6.

The sections below highlight the disease areas showing most promise for PGS implementation (7.1), followed by a summary of some networks and organisations involved with PGS within and between countries, and studies from around the world that can inform our approach to PGS implementation. This discussion is divided into the international (7.2) and the Australian landscapes (7.3). It is by no means an exhaustive review, but the studies discussed illustrate the main health conditions being investigated and the types of studies that can help to inform implementation of PGS into Australian healthcare. We also acknowledge there is a wealth of research underway to gather genomic data from GWAS, through biobanks and other studies and to develop methods to improve the prediction accuracy of PGS for a variety of clinical purposes and contexts, applicable across populations. Biobanks (such as UK Biobank) provide access to large databases, often containing genomic and other health data, that Australian researchers can and are already using in PGS research. However, this area of discovery research is not the focus of this report.

7.1 Health conditions under active investigation for PGS implementation

As described earlier, the clinical utility of a particular PGS is dependent on the health condition and the purpose for which it is being used. The use of PGS in risk assessment or clinical management of some common conditions, responsible for a significant burden of disease in the population, is further along the path to implementation for a variety of reasons. These include the prevalence and heritability of the condition, existing screening protocols (either at a population level or in primary

care), having a well-developed PGS test (clinical validity) that can be incorporated into clinical risk tools, and existing interventions that can result in improved health outcomes.

Breast cancer

Breast cancer is the most commonly occurring cancer worldwide[7]. It has a strong hereditary component but much of the heritability remains unexplained. Single high-risk genes (such as BRCA1 and BRCA2) explain about 25% of familial risk (48). GWAS have identified >180 independent common genetic variants that together account for ~20% of the familial relative risk of breast cancer and ~40% of the heritability attributed to all common variants on genome-wide SNP arrays (49, 50), although non-genetic risk factors in total account for more variation than genetic risk factors. In addition, SNPs have been discovered that can identify breast cancer subtypes i.e., women who have an increased risk of developing ER^+ or ER^- breast cancers (51).

Considerable research is being done in Australia and internationally to explore the use of PGS in both population screening and clinical settings with the focus on inclusion of PGS into existing risk prediction models (52). These models combine genetic data (high-moderate single risk genes and PGS), family history information, breast pathology, hormonal, anthropometric and lifestyle factors to create a personalised breast cancer risk score (e.g., the CanRisk tool (53)). Cancer screening is subsequently stratified according to risk. Personalised approaches to the prevention or early detection of breast cancer have emerged as highly promising strategies and randomised controlled trials (RCTs) are underway (54).

PGS in breast cancer has the potential to be used in a variety of public health and clinical contexts (54-56), including:

- Risk-stratified population screening (e.g., different frequency of screening, age thresholds for screening initiation or screening modalities (mammography, MRI, ultrasound)).
- Personalising risk estimates in families with a high risk of breast cancer in the familial cancer clinic setting (e.g., to refine risk for individuals who test negative for pathogenic variants in high/moderate risk genes or modifying risk in those who test positive to these genes).
- Guiding risk-reducing interventions and enhancing shared decision-making (e.g., decisions about preventive mastectomy or preventive medications in high-risk women).
- To help differentiate between subtypes of breast cancer and prognostic outcomes, such as the risk of contralateral disease (54, 56).

To support these potential clinical applications, acceptability of PGS by individuals and health professionals, communication of PGS risk information, and the psychological and behavioural responses to receiving such information are under investigation (55).

Cardiovascular disease

Cardiovascular disease (CVD) is the leading cause of death in Australia and the leading cause of morbidity and mortality globally (57). It is not fully explained by traditional risk factors (58). The heritability of coronary artery disease (CAD) is high, estimated to be between 40% and 60% (59).

[7] World Cancer Research Fund International, 2022. Accessed at: https://www.wcrf.org/cancer-trends/breast-cancer-statistics/ on 21 July 2022

PGS models have been developed for several CVD, including CAD (also called coronary heart disease) and stroke, as well as intermediate causes of CVD, such as atrial fibrillation, hypercholesterolaemia and hypertension (47); however PGS for CAD are the most developed (47, 60-62).

The use of PGS in CAD has good potential because: CAD is the most common form of heart disease and the burden of disease in the population is high; CAD has a high heritability; there are large international consortia working on GWAS with the validation of 163 loci associated with CAD explaining 30-40% of observed heritability (63); there are existing risk tools combining multiple risk factors; and there are effective medical and behavioural interventions (47, 58, 60, 61). Moreover, there is some evidence for clinical benefit from including PGS information for risk stratification, including a greater benefit from statin therapy for primary or secondary prevention for those with a high PGS (60, 61). However, the impact of a PGS-based risk result on preventive health behaviours compared to already existing risk assessments has not yet been established, although a recent study showed web-based communication of an atherosclerotic CVD PGS score resulted in some positive behaviour change and propensity to seek care in middle-aged people (64).

Other cancers

Melanoma

Melanoma cases and deaths are projected to double across the world in the next 20 years (65). In Australia melanoma is the third most diagnosed cancer[8], but there is no population screening program. As exposure to UV radiation is the main risk factor, primary prevention relies on health promotion strategies to reduce sun exposure. Melanoma also has a large genetic component (66).

Identifying people at high risk of melanoma is the focus of research to facilitate targeted screening, surveillance and behavioural counselling (67). Common genomic variants have been identified that combined as a PGS perform at least as well as other measures of melanoma risk, such as skin type or family history, and can help to identify those at risk who may not have these other risk factors (68, 69).

The acceptability, feasibility and behavioural impact of personalised genomic information for melanoma risk have recently been investigated by Australian researchers (42, 70-73).

Colorectal cancer

Colorectal cancer was the third most diagnosed cancer in 2017 and the second leading cause of cancer death in Australia in 2019[9]. Colorectal cancer is highly preventable and screening to detect early signs of cancer (pre-cancerous polyps) is the key to prevention. However, uptake of the National Bowel Screening Program in Australia is well under 50% (74), partly due to inaccurate perceptions of risk (75). On the other hand, people at average risk of colorectal cancer are undergoing unnecessary colonoscopies with associated physical and economic effects (76). Risk

[8] AIHW. Cancer Data in Australia, 2022. Accessed at: https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/cancer-rankings-data-visualisation on 11 August 2022

[9] Cancer Australia. Bowel cancer (Colorectal cancer) in Australia statistics. Accessed at: https://www.canceraustralia.gov.au/cancer-types/bowel-cancer/statistics on 25 July 2022

stratification is increasingly being used to increase the effectiveness of colorectal cancer screening, which is currently based on family history and age (77).

Risk factors for colorectal cancer include family history, environmental exposures (diet, smoking, obesity) and genetic factors (including high-risk variants and common SNPs). Genetic testing for high-penetrance genetic variants (e.g., Lynch syndrome) in familial cancer clinics has been available for many years but applies to only a small proportion of the population. Common variants associated with colorectal cancer have been identified and PGS have been tested in case-control studies (78-81). The potential of PGS models for risk stratification is being investigated by groups around the world, including Australian researchers (45, 82), but there are a range of issues to be resolved before they are ready for clinical implementation, and larger trials are necessary (83).

Prostate cancer

Prostate cancer is the most diagnosed cancer in Australia as a whole and among males[10]. Although it doesn't have a high case-fatality rate, prostate cancer was the second most common cause of cancer death among males in 2019[11]. Risk factors for prostate cancer include age and family history with higher risk for men carrying pathogenic BRCA1/2 mutations (12). The main screening test for prostate cancer is prostate specific antigen (PSA), which has been shown in many trials to lead to overdiagnosis and over treatment (84).

PGS for prostate cancer risk have been developed to guide clinical follow-up (such as prostate biopsy) of a PSA test result using PGS-adjusted PSA levels (85). This study suggests PGS-adjusted PSA could avoid up to 20% of negative prostate biopsies and the associated risks of the procedure (85).

Diabetes

The prevalence of Type 2 diabetes is high in Australia and around the world and is increasing[12]. Type 1 diabetes is less common, but it has a younger age of onset and a more severe phenotype, requiring different treatment options (86). There are also other types of diabetes with intermediate phenotypes (86).

Type 1 diabetes

Type I diabetes is highly heritable, with 80% of the susceptibility genes identified (86). A 67-SNP PGS has high accuracy and is transferable across ancestries (87). PGS for type 1 diabetes have the potential to predict at-risk children most likely to progress to disease and for discriminating between types of diabetes (87-89). PGS to identify infants at high risk of developing type 1 diabetes are at the stage of clinical trials (see sections 7.2 and 7.3).

[10] AIHW. Cancer Data in Australia, 2022. Accessed at: https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/cancer-rankings-data-visualisation on 11 August 2022

[11] Cancer Australia. Prostate cancer in Australia statistics. Accessed at: Cancer Australia. Accessed at: https://www.canceraustralia.gov.au/cancer-types/prostate-cancer/statistics on 25 July 2022

[12] Diabetes in Australia/ Globally. Accessed at: https://www.diabetesaustralia.com.au/about-diabetes/ on 27 July 2022

Type 2 diabetes

Type 2 diabetes is caused by a combination of genetic, epigenetic and environmental factors, but only a small proportion of the total heritability has been explained (86). PGS for the prediction of Type 2 diabetes have been developed (90). However, despite dozens of gene variants discovered from GWAS, the effect of each SNP is weak and environmental factors the main drivers of type 2 diabetes development (90). Potential uses include adding PGS to existing risk models and estimating lifetime risk trajectories, but clinical utility is not established (12). There may also be potential for PGS in predicting treatment response and risk stratification for diabetes complications (61).

Glaucoma

Glaucoma is a leading cause of vision loss among adults in Australia and globally and remains undiagnosed in about 50% of people (91). Although timely intervention can slow or stop progression of vision loss, there is no screening program for glaucoma and early diagnosis can be difficult. Thus, identifying those at risk of glaucoma is a priority. Risk factors for glaucoma include family history, where first degree relatives have up to a 10-fold increase in risk (91) and heritability has been shown to be high (92). PGS have been developed that show promise in predicting earlier onset of glaucoma, an increased risk of developing advanced glaucoma, and glaucoma requiring surgical intervention (93, 94).

Mental health disorders

Mental health disorders include common complex disorders with high heritability, and they can be difficult to diagnose and treat effectively (95). Risk variants have been identified for various mental health disorders, including major depression (96, 97), schizophrenia and bipolar disorder (56, 97), and Alzheimer's disease (12, 98). Examples of the potential clinical utility of PGS in mental health disorders are in facilitating diagnosis and prognosis in schizophrenia and bipolar disorder (56), helping to predict age of onset of Alzheimer's disease (12) and guiding treatment decisions (16, 97). Murray et al, 2021 (97) argue that application of PGS in psychiatry is more likely to be in the context of young people presenting in a prodromal stage (with symptoms not yet commensurate with a formal diagnosis), where high PGS could aid clinical decision making. Given that biomarkers are particularly lacking in psychiatry (99), development of an evidence base for utility of PGS is particularly critical, although there are particular sensitivities in this area of research.

7.2 International best practice, approaches and health system integration[13]

Networks, consortia and organisations supporting PGS implementation

Table 1 lists some of the main networks and organisations either currently or potentially involved in PGS. Given their largely public health systems, PGS implementation research and education

[13] To determine the scope of international research and implementation of PGS, we undertook desktop research of the main bodies involved in PGS work in the USA, the UK, Europe and Asia, as well as multinational collaborations. We also identified national and multinational networks working in this area that may be useful as models for work in Australia or as partners in research or investment. A literature search identified seminal research publications and commentaries by

initiatives in the UK and, to a lesser extent, in Europe may have more relevance to PGS implementation in Australia. With a complex, largely private health system, US networks may offer more to Australian researchers with respect to access to large GWAS cohorts needed for PGS development.

Table 1: Networks and organisations involved in PGS research and implementation

Network/Organisation	Purpose
United Kingdom	
PHG Foundation https://www.phgfoundation.org	A health policy think-tank and charity of the University of Cambridge. The Foundation aims to achieve better health through the responsible and evidence-based application of biomedical science.
NHS* Health Education England (HEE) Genomics Education Programme https://www.genomicseducation.hee.nhs.uk	Aims to deliver and advise on learning and development opportunities that prepare current and future NHS professionals to make the best use of genomics in their practice. Could develop PGS education.
Genomics England https://www.genomicsengland.co.uk/genomic-medicine	Set up by the Department of Health & Social Care in 2013, it aims to enable others to deliver genomic healthcare and conduct genomic research.
Our Future Health https://ourfuturehealth.org.uk	Aims to give researchers from universities, charities, the NHS and others an opportunity to discover and test more effective ways to predict, detect and treat common diseases such as dementia, cancer, diabetes, heart disease and stroke.
UK Biobank CardioMetabolic Consortium CHD Working Group	To assess the use of self-reported and hospital record data on CAD in UK Biobank and define the relevant case & control groups for genetic analyses of CAD risk.
Europe	
'1+ Million Genomes' (1+MG) https://digital-strategy.ec.europa.eu/en/policies/1-million-genomes	The 1+MG initiative aims to enable secure access to genomics and the corresponding clinical data across Europe for better research, personalised healthcare and health policy making.
European Collaborative on Personalized Early Detection and Prevention of Breast Cancer (ENVISION)	ENVISION brings together several international research consortia working on different aspects of the personalized early detection and prevention of breast cancer (52).
United States of America	
National Human Genome Research Institute (NHGRI)	The mission of the NIHGRI is to accelerate scientific and medical breakthroughs that improve human health by

international experts in PGS research and implementation. Other articles were identified through reference searches and advice from the Project Strategy Group.

https://www.genome.gov/Health/Genomics-and-Medicine/Polygenic-risk-scores	driving research, developing new technologies, and studying the impact of genomics on society.
eMERGE Genomics Risk Assessment and Management Network https://www.genome.gov/Funded-Programs-Projects/eMERGE-Genomics-Risk-Assessment-and-Management-Network	This is the 4th phase of the eMERGE Network, a national network organized and funded by the NHGRI, started in 2007. It brings together researchers with expertise in genomics, statistics, ethics, informatics, and clinical medicine from research institutions to conduct research in genomics using electronic medical records, including discovery and clinical implementation.
ClinGen Complex Disease Working Group https://clinicalgenome.org/working-groups/complex-disease/	The Working Group is working towards promoting standards in polygenic and integrated risk score development and reporting of results to enable assessments of validity and utility.
Clinical Sequencing Evidence-Generating Research (CSER) consortium https://cser-consortium.org	A multi-site research program funded by the National Human Genome Research Institute (NHGRI), the National Cancer Institute (NCI) and the National Institute on Minority Health and Health Disparities (NIMHD).
The All of Us Research Program https://allofus.nih.gov/	Led by the NIH, All of US aims to gather data from one million or more people from all life stages living in the US to accelerate research and improve health. Researchers will have access to these data to study differences in lifestyle, environment, and biology.
Multinational	
Polygenic Risk Score Task Force of the International Common Disease Alliance (ICDA) https://www.icda.bio	A multidisciplinary group comprising experts in genetics, law, ethics, behavioural science and other relevant areas. The ICDA is a forum to develop ideas and plans to accelerate progress in common disease genetics discovery and translation.
The Global Alliance for Genomics and Health (GA4GH) https://www.ga4gh.org	Formed in 2013, an international, non-profit alliance of 600+ organisations working in healthcare, research, patient advocacy, life science, and information technology working to create frameworks and standards to enable the responsible, voluntary, and secure sharing of genomic and health-related data.
INTERVENE https://www.interveneproject.eu	An international consortium that seeks to develop and implement tools for AI-facilitated personalised medicine. The consortium consists of 17 research and other organisations representing 7 EU members states (Finland, Germany, Italy, Estonia, Austria, Belgium, the Netherlands) and Norway, UK and USA.

* NHS: National Health Service, UK

United Kingdom

The potential for polygenic scores to inform more targeted prevention and treatment through increased 'risk stratified' screening is now part of the policy agenda in the UK (100). One of the main groups helping to put that policy into action is the *PHG Foundation*. They are leading the work in the UK with respect to methods for assessing the clinical utility of PGS (18) and the steps needed for implementation of PGS into practice (17); PGS and personalised risk for breast cancer (55); and PGS in screening for CVD risk (62), including a model for implementation into the NHS (47).

Providing education opportunities for healthcare professionals to learn about PGS will be required for implementation in clinical practice. The NHS Health Education England (HEE) Genomics Education Programme delivers and advises on education to prepare current and future NHS professionals to make the best use of genomics in their practice. Although not currently focused on PGS specifically, HEE is well placed to develop and deliver PGS education (47).

Our Future Health is a collaboration between the public, charity and private sectors and will perform up to five million polygenic risk score assessments on volunteers, who will each be offered personalised feedback on their results (47). It will link phenotypic data to longitudinal biological samples and be available for research purposes to discover and test more effective ways to predict, detect and treat common diseases such as dementia, cancer, diabetes, heart disease and stroke. The program is designed to reflect the UK population, including groups of people that have previously been under-represented in health research.

Genomics England supports genomics research (including the 100,000 Genomes project[14]) and healthcare delivery in the UK but is not specifically focused on PGS. *Genomics England Clinical Interpretations Partnership* is a community of approved researchers from around the world with access to the Genomics England Research Environment, to do research on de-identified datasets in the National Genomics Research Library. The aim of the partnership is to enable scientific discovery and accelerate its translation into patient care. This could potentially involve PGS research.

Amongst their projects, the *UK Biobank CardioMetabolic Consortium CHD Working Group* used a meta-analytic approach to develop a genomic score for CAD and tested it in more than 480,00 individuals from the UK Biobank (101).

Europe

Individual research groups across Europe are actively working on various aspects of PGS research and some European Union (EU) initiatives are underway to support this work, such as the *1+ Million Genomes initiative (1+MG)*. The aim of 1+MG is to enable secure access to genomics and clinical data across Europe for better research, personalised healthcare and health policy making. Twenty-two EU countries, the UK and Norway have agreed to increase efforts towards creating a European data infrastructure for genomic data and implementing common national rules enabling federated data access. The generation of comparable evidence across European countries is strongly encouraged to help translate genomic innovation into effective and cost-effective healthcare, as well

[14] See: https://www.genomicsengland.co.uk/initiatives/100000-genomes-project

as improving the sharing of results. European countries such as Finland and Estonia also have biobanks used primarily for GWAS and PGS development, but also for studies assessing the impact of providing PGS results to participants (e.g., (64)).

We could not identify many formal research networks working exclusively within Europe, except for the *European Collaborative on Personalized Early Detection and Prevention of Breast Cancer (ENVISION)*. This brings together several international research consortia working on different aspects of the personalised early detection and prevention of breast cancer (52). In a consensus conference in 2019, priority research areas were identified: 1) breast cancer subtype-specific risk assessment tools applicable to women of all ancestries; 2) intermediate surrogate markers of response to preventive measures; 3) novel non-surgical preventive measures to reduce the incidence of breast cancer of poor prognosis; and 4) hybrid effectiveness-implementation research combined with modelling studies to evaluate the long-term population outcomes of risk-based early detection strategies. Importantly, ENVISION encourages the use of research designs that reduce the time lag between evidence generation and implementation, with a shift away from small studies with hypothetical scenarios to multidisciplinary research with engagement of all stakeholders to ensure a systems approach to implementation studies (52).

United States of America

The health system in the USA is complex and care is often delivered by private health companies to individuals with private health insurance. PGS is not routinely used across the health system but is available through private laboratories who are offering a variety of PGS tests on a user-pays basis (102). However, there is a great deal of research and funding directed to all aspects of PGS research, from the laboratory to translation. Precision medicine is a focus of the US government with the launch of the *Precision Medicine Initiative* by President Obama in 2015. This long-term research endeavour involves the National Institutes of Health (NIH) and other research centres, and aims to understand how genetics, environment, and lifestyle can help determine the best approach to prevent or treat disease. In the short-term the focus on cancer research but in the longer term, the goal is to bring precision medicine to all areas of health and healthcare on a large scale.

To this end, the NIH has launched the *All of Us Research Program* (29), which involves at least 1 million volunteers from around the USA. Participants provide genetic data, biological samples, and other health information. To encourage open data sharing, participants can access their health information, as well as research that uses their data, during the study. Researchers can use these data to study a large range of diseases, with the goals of better predicting disease risk, understanding how diseases occur, and finding improved diagnosis and treatment strategies. In March 2022, the study released its first genomic dataset for use by researchers.

Much of the genomics and PGS research in the USA is funded by the National Human Genome Research Institute (NHGRI, part of the NIH). The *eMerge Genomic Risk Assessment and Management Network* (July 2020 - April 2025), funded by the NHGRI, includes ten clinical sites and seeks to understand how best to validate and implement genome informed risk assessments (a combination of genomic, family history, and clinical risk factors). The Network is investigating whether these risk assessments for selected conditions can be generated reliably across diverse populations and help

inform clinical decisions about management of patients at risk. The Network aims to: calculate and validate polygenic scores in diverse populations for 10 conditions; combine PGS results with family history and clinical covariates; return results to 25,000 diverse participants; and assess understanding of the risk assessments, uptake of corresponding recommendations for management of disease risk, and impact on clinical outcomes in a prospective cohort study.

The *Clinical Sequencing Evidence-Generating Research (CSER)* consortium aims to develop and share best practices in areas such as the discovery and interpretation of genomic variants, return of results, healthcare utilisation, health outcomes and metrics, and the ethical, legal, and social implications of sequencing in diverse populations. CSER's seven clinical sites seek to study the effectiveness of integrating genome sequencing into the clinical care of diverse and medically underserved individuals.

The Implementing GeNomics In pracTiCe (IGNITE) Pragmatic Clinical Trials Network is an NIH-funded network dedicated to supporting the implementation of genomics in healthcare. The network is not yet working in PGS but this may be within their remit.

The ClinGen Complex Disease Working Group is part of ClinGen (Clinical Genome Resource), funded primarily through the NHGRI. ClinGen aims to build a central resource of genes and variants for use in precision medicine and research, mostly with respect to monogenic conditions. However, the *Complex Disease Working Group* states its purpose as: How can we promote standards in polygenic and integrated risk score development and reporting of results to enable assessments of analytic validity, clinical validity, and clinical utility? In partnership with the PGS Catalog, the Working Group has developed reporting standards for polygenic scores in risk prediction studies (103).

Multinational Networks

The *Polygenic Risk Score Task Force of the International Common Disease Alliance (ICDA)* is a multidisciplinary group comprising experts in genetics, law, ethics, behavioural science and other areas. The ICDA is a forum to develop ideas to accelerate progress in common disease genetics discovery and translation. Much of this work is done by Working Groups aiming to: define and prioritise key needs and opportunities; undertake pilot projects designed to address key hurdles and develop proposals for implementing necessary infrastructure; translate scientific needs into technical and policy requirements; and facilitate implementation of infrastructure within and across organizations to meet those requirements. In 2021, the Polygenic Risk Score Task Force (26 authors from 8 countries) published a comprehensive paper on the benefits, risks and gaps for use of PGS in the clinic (13).

In support of their aim to support safe sharing of data, the *Global Alliance for Genomics and Health (GA4GH)* published the *Framework for Responsible Sharing of Genomic and Health-Related Data* in 2014 (re-affirmed in 2019) that can be used to guide projects around the world.

The *INTERVENE consortium* (coordinated by the University of Helsinki) involves biobanks and medical repositories that are linked to cross-disease health registries or electronic health records. The consortium partners will link relevant data from the FinnGen study, the Estonian Biobank, the HUNT study, the Network for Italian Genomes, Partners Biobank, HUS Helsinki Biobank, UK Biobank,

and Genomics England providing more than >1.7 million genomes linked with electronic health records and registry data.

Other countries

The *Canadian Institutes of Health Research (CIHCR)* doesn't appear to be involved in PGS implementation but does have an interest in representing diversity of the Canadian population in genomic data, including PGS. The *CIHR Institute of Genetics* is committed to ensuring GA4GH standards and principles will be used to enable national and international data sharing. Genome Canada is mainly looking at genomics applications for rare diseases, although it is funding a study on personalised risk assessment for breast cancer (see Table A1, Appendix 1), and most likely other PGS studies, through its project grants.

Singapore has a 10-year *National Precision Medicine* strategy and Precision Health Research Singapore (https://www.npm.sg) is the central entity set up to coordinate the implementation of Phase II of the 10-year plan. Precision Health Research Singapore has a grant stream called the Clinical Implementation Pilot (PRECISE CIP) Fund designed to support projects for the clinical application of genetic/genomic tests to diagnose, manage and/or treat a specific patient cohort and/or population. A study (SPECTRA) from the SignHealth Duke-NUS Institute of Precision Medicine (PRISM) aims to enrol 10,000 Singaporeans to undergo whole genome sequencing (104).

The *Human Heredity and Health in Africa (H3Africa)* consortium (https://h3africa.org) facilitates research into diseases on the African continent while also developing infrastructure, resources, training, and ethical guidelines to support African research led by African scientists. The initiative consists of 51 African projects that include population-based genomic studies of common, non-communicable disorders as well as communicable diseases. A recent publication arising from H3Africa investigated the transferability of risk scores to African populations, finding risk scores derived from African American individuals enhanced polygenic prediction of lipid levels for sub-Saharan Africans compared to scores derived from European or multi-ancestry studies (105).

Professional associations and PGS

Few international professional associations have published position statements or viewpoints on the use of PGS in healthcare.

- The *European Society of Human Genetics (ESHG)* has no official position on the use of PGS in the context of common diseases in adults. However, in response to private companies offering PGS testing of embryos as part of pre-implantation genetic testing, the EHSG has warned that the use of PGS in this context is unproven and unethical (106).
- The *European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) Expert Consensus Statement on the state of genetic testing for cardiac diseases* has a section describing the research on PGS for cardiac disease but states that it is too early for PGS to be used in clinical practice and has no practice recommendations (107).
- The *American Heart Association* has issued two scientific statements: one (2021) discussing how to include marginalised racial and ethnic groups in genetic and genomic CVD research

(26); and the other (2022) gives an overview of PGS for CVD along with provisional guidance to health care professionals, researchers, policymakers, and patients related to five cardiometabolic diseases (61).

Databases and tools to facilitate research and implementation

It is widely agreed that PGS research will be best served by being collaborative and open with standardised methods for developing and reporting GWAS data and polygenic scores. Further along the path to implementation is the need for tools incorporating PGS information to use in the clinic. The resources listed in Table 2 are a selection of collaborative efforts that can be used by researchers from around the world.

Table 2: A selection of tools and databases for PGS research

Resource	Purpose
GWAS Catalog https://www.ebi.ac.uk/gwas/home	The NHGRI-EBI GWAS Catalog is a publicly available resource of GWAS and their results.
Genome Aggregation Database https://gnomad.broadinstitute.org/	gnomAD is a coalition of investigators seeking to aggregate and harmonize exome and genome sequencing data from a variety of large-scale sequencing projects, and to make summary data available for the wider scientific community. Mainly funded by the Broad Institute (USA).
The Polygenic Score (PGS) Catalog https://www.pgscatalog.org	An open database of published PGS. Each PGS is consistently annotated with relevant metadata; including scoring files (variants, effect alleles/weights), annotations of how the PGS was developed and applied, and evaluations of their predictive performance. PGS Catalog co-authored a paper on reporting standards for PGS (103).
Cancer PRSweb https://prsweb.sph.umich.edu:8443	An online repository of PGS for 35 common cancer traits integrating summary statistics from published GWAS, the NHGRI-EBI GWAS Catalog, and UK Biobank-based GWAS (108). Summary statistics have been condensed into PGS using various approaches and validated in two biobanks with respect to predictive performance and discrimination. It also features phenome-wide PGS association study results (PRS-PheWAS) for predictive PGS.
CanRisk tool www.canrisk.org	Developed by the Centre for Cancer Genetic Epidemiology and hosted on a University of Cambridge virtual server, the CanRisk tool applies the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) in a web-based tool. The current version of BOADICEA includes genetic (high-risk genes and polygenic risk scores) and non-genetic risk factors. It has been

	evaluated for acceptability by clinicians (109) and has been updated according to the feedback (53).
KardioKompassi tool https://kardiokompassi.fi	Developed by the Institute for Molecular Medicine Finland (FIMM), University of Helsinki, this tool estimates the risk for coronary heart disease and/or stroke over the next 10 years by combining traditional health information with genetic risk information. Also allows users to explore how changes to modifiable risk factors affect their risk (64)

International studies assessing clinical utility of PGS

It should be noted that the review of international PGS research below is not exhaustive. However, it covers a range of studies and study types that either currently or in the near future will provide evidence to inform PGS implementation in some of the major health conditions and contexts.

Large trials

The main health conditions currently being investigated in large clinical trials or prospective cohort studies are breast cancer and CVD (mostly CAD), plus one large US study investigating the effects of delivering PGS risk estimates for five conditions and a trial of screening for risk of type 1 diabetes.

To examine the potential for risk-based **population screening for breast cancer**, several large trials and prospective cohort studies are underway in Europe (MyPeBS), the USA (GENRE2, WISDOM), the UK (BC-Predict), Singapore (BREATHE), Spain (DECIDO) and Canada (PERSPECTIVE I&I). (See Table A1, Appendix 1 for study details). Six of these studies are designed to provide evidence to inform the inclusion of PGS in population screening (110-115) and one trial is looking at the effect of PGS information on the uptake and ongoing use of preventive medications for women found to be at high risk of breast cancer using a risk tool that includes a PGS (116). In addition to health and behavioural outcomes, most studies are measuring aspects of ethical, psychological and socio-economic impacts of providing personalised breast cancer risk information. Three studies include health economic components (111, 113, 115). Results from these studies should be published in the next few years and will provide vital data about the utility of breast cancer PGS in population health contexts.

The *PEPRS2 study*[15] (USA) aims to recruit 10,000 people to investigate whether knowledge of the degree of **CAD genetic risk** or **glaucoma genetic risk** (using a PGS) influences patient and physician decision-making as well as clinical outcomes during short-term (6-month/2-year) and long-term (3/5-year) follow-up. A CAD and glaucoma PGS will be calculated for all study participants, with participants randomized to receiving either their CAD or glaucoma PGS. The design is informed by a pilot study (PEPRS1) and uses the MyGeneRank smartphone application developed previously (41).

[15] See: https://clinicaltrials.gov/ct2/show/NCT05175651

The *GeneRISK Study*[16] (coordinated by the Institute for Molecular Medicine Finland) is an ongoing prospective observational study focusing on **genetic risk factors of CVD** and on utilising genetic information in preventing diseases. The main goal of the study is to test the longitudinal impact of communicating personal genome-based disease risk information directly to the study participants. 7,342 randomly selected 45- to 65-year-old individuals were recruited during 2015-2017 and follow-up is continuing.

The *Genomic Medicine at Veterans Affairs (GenoVA) Study*[17] is a US RCT in which patients and primary care physicians receive a clinical PGS laboratory report on five conditions: **CAD, type 2 diabetes, atrial fibrillation, colorectal cancer, and prostate cancer (males) or breast cancer (females)**. Eligible patients are aged 50 to 70 years and have no known diagnoses of these five conditions. The objectives are to observe how PGS affects existing disease screening and diagnosis paradigms and whether it increases detection of undiagnosed prevalent or incident disease. So far, the processes leading to the development and validation of a genotype-array-based clinical assay for six PGS and the reporting of results to patients and primary care physicians have been published, along with results from the first 227 prospective samples (20). An important aspect of this study is that it provides a model for developing workflow systems, from assay development to laboratory reporting to patient and physician information, that could be tailored for the Australian healthcare system and for specific PGS contexts (20).

A very large cohort study (the Freder1k-Study[18]) is underway in Germany to test a PGS for **type 1 diabetes** in neonates and infants. The target is to enrol 318,000 infants, with the aim to trial early therapies to prevent beta-cell autoimmunity and type 1 diabetes in those found to be at > 10% risk for developing type 1 diabetes.

Small trials and pilot implementation studies

The *Healthcare Evaluation of Absolute Risk Testing (HEART)* study[19] is a potentially important demonstration project to assess the utility of a **CVD risk** tool including a PGS in primary care. A collaboration between the NHS and Genomics PLS, the study aims to test 1,000 healthy volunteers aged between 45 and 64, recruited through general practices in the north of England. The HEART study will test the addition of a PGS to the QRisk analysis (QRisk estimates the chance that a person is likely to be affected by CVD in the next decade by using a combination of risk factors). The level of risk determined by the QRisk result will inform advice regarding lifestyle changes and the use of statins to decrease risk of CVD. The approach being tested may be a model for primary care settings and be applied to other common conditions. The study is currently listed on the trials.gov site as "active, not recruiting".

[16] See: https://thl.fi/en/web/thl-biobank/for-researchers/sample-collections/generisk-study

[17] See: https://clinicaltrials.gov/ct2/show/NCT04331535

[18] See: https://www.clincosm.com/trial/freder1k-testing-infants-type-1-diabetes-risk

[19] See: https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/the-heart-study-and-version-10/

The *Genetic Risk-Based **Atrial Fibrillation Screening** (GeneAF)*[20] from the Montreal Heart Institute is listed as recruiting in June 2021 with no updates since then. The study aims to determine whether the published genome-wide polygenic scores for atrial fibrillation (GPSAF) can facilitate AF screening by accurately discriminating between patients with low and high risk for AF.

Some small trials of the use of **PGS in CAD** have been published (40, 117-120). The MI-GENES RCT included outpatient clinic attenders (n=203) at moderate risk of CAD (40). By the 6-month follow-up, LDL-cholesterol levels were lower, and statins had been initiated more often, in those receiving 10-year CAD risk information including a genetic risk score compared to those who received a conventional 10-year risk score only, despite diet and physical activity levels remaining unchanged (40). In contrast, a small (n=94) pilot RCT of a PGS intervention versus standard care showed no change in LDL-cholesterol levels and other outcomes by 6 months follow-up in people at moderate risk of CAD (117). The INFORM RCT (n=956 people aged 40-77 years with no history of CVD randomised to 4 groups) showed that provision of CAD risk information, whether it was based on phenotype alone or phenotype and PGS, along with web-based lifestyle advice did not result in changes in physical activity or health-related behaviours over 12 weeks follow-up (120).

A pilot RCT of 1) patients with cardiomyopathy or 2) apparently healthy individuals in a primary care setting gave whole genome sequencing results, including PGS for **eight cardiometabolic conditions**, to those in the intervention arms (n=50 for each patient group) compared to assessing risk through family history alone (the MedSeq Project) (119). One aim of the study was to assess health behaviour changes at 6 months follow-up. Results showed no psychological harm from the genomic information and some suggestion that high-risk PGS scores motivated behaviour change (118). There is wide discussion about the need for larger trials and to define the specific clinical contexts in which PGS for CAD will be useful (47, 60-62, 121, 122). The large trials underway (above) may help to answer some questions. However, hybrid implementation study designs should be considered for more timely results that can keep pace with this rapidly changing field (58).

Health economic studies

The health economic components of the studies in Table A1 (Appendix 1) will provide important evidence for implementation of risk-based **breast cancer screening**. So far, cost-effectiveness and benefit-to-harm studies for risk-stratified breast cancer screening have been based on hypothetical modelling only (123, 124).

A few cost-benefit and cost-effectiveness studies have been published for use of **PGS in CVD** (reviewed in Gladding et al, 2020 (60)) with varying conclusions regarding potential cost-effectiveness. A Finnish study recommends genomic testing could be cost-effective only if targeted for use in very specific circumstances (125). A recent study based on UK Biobank participants at intermediate CVD risk suggested PGS-guided statin therapy could be cost-effective, particularly if the costs of PGS decrease in the future (126). However, more work needs to be done to show benefit in a variety of clinical scenarios.

[20] See: https://clinicaltrials.gov/ct2/show/NCT04932798

Limited cost-effectiveness modelling has been done for use of PGS for personalised risk screening in **colorectal cancer** (127) and **prostate cancer** (128). Cost-effectiveness of a PGS for use in population-wide screening for primary open-angle **glaucoma** has been modelled for Australia and the UK (129).

Understanding of PGS, behaviour change, public & professional views

The evidence from large-scale clinical trials will take some years to collect and feed into clinical practice, and there are many challenges to address before widespread implementation of PGS. For breast cancer, these range from evaluation of risk tools through to patient understanding and uptake of preventive behaviours or interventions (55). For example, although PGS for breast cancer have been offered by two diagnostic laboratories since 2017, a survey of cancer genetic counsellors in the USA showed less than half have ordered a test and of those who have, only a third said it changed clinical management, citing lack of clinical guidelines, insufficient evidence for clinical utility and lack of tests for women of non-European ancestry (130). A UK study has also identified anticipated barriers for British-Pakistani women in potentially accessing risk-stratified breast screening (131). We also need to understand the views of policy decision-makers if protocols for screening programs are to change (132). Similar challenges apply to PGS in other health conditions. Research has and is being done in many countries to bring the views of the public, patients, health professionals and policy makers to implementation planning for a range of PGS contexts (55, 132-135). Australian researchers are leaders in some aspects of this work (see Section 7.3).

Summary

Despite the extensive work going on in many countries across all aspects of PGS research and implementation, there are still many challenges around infrastructure needs, gathering the evidence and providing resources for translation from research to healthcare, ethical and regulatory issues, and social issues. Different countries are at different stages along the path of implementation of PGS into public health and clinical practice. However, studies designed to demonstrate clinical utility of PGS in various contexts are underway and evidence is accruing, which will help to inform research and implementation in Australia. The international networks/collaborations and PGS support platforms may also assist Australian researchers.

In Australia, we need to consider PGS and the research to support implementation according to our health system and public health and clinical contexts, and within our research and health system resources. Section 7.3 summarises the current PGS research in Australia and highlights the areas where Australian research is most advanced.

7.3 PGS research and implementation in Australia[21]

Researchers from across Australia are making valuable contributions to the PGS field, from basic science research (GWAS studies and PGS development; related to complex diseases as well as

[21] To determine the scope of Australian research and implementation of PGS, we undertook desktop research of published studies, published expert opinion, activities of professional bodies and informal consultation with prominent researchers and practitioners in the field of genomics and PGS.

refining risk in Mendelian disorders), to clinical, psychosocial and health communication research. The basic science research is often done in collaboration with overseas researchers, using international databases and biobanks. Australia has some leading research groups in all aspects of PGS research and we are making a particularly strong contribution to the psychosocial and health communication aspects, as well as behavioural responses to PGS information.

Appendix 2 lists a selection of studies funded by the National Health and Medical Research Council (NHMRC; Table A2) and the MRFF (Table A3) that we could identify as investigating PGS. They show the breadth of work underway in Australia in recent years, particularly in the area of CAD and cancers. There are likely to be other studies with a PGS component as part of a program of research that were not identified in our search, as well as studies being conducted within individual institutions with other sources of funding.

Networks and consortia

National networks

We could not identify any formal Australian networks with the specific aim to support or promote PGS research to inform implementation. However, there are many research collaborations across universities and research institutions around Australia working on PGS projects, often within the context of a particular health condition, such as melanoma or breast cancer.

Australian Genomics is a national collaboration funded by the federal government that supports the translation of genomic research into clinical practice (136). Although the current focus of Australian Genomics is the application of genomics in diagnosing and managing monogenic conditions, it has undertaken this PGS incubator project to inform research in PGS with a focus on implementation.

The Australian Cardiovascular Alliance (121) has potential to work in this space. Professor Gemma Figtree is one of the leaders of the network and she has authored a paper describing what needs to happen for clinical implementation of PGS for CAD, with a “call to arms” to collect the required evidence (58).

Australian research collaborations with international networks

Many Australian research groups working in genomics and PGS have links to international researchers or international networks, some formal collaborative networks, and other project-based collaborations. Examples include:

- *Melanoma:* A research team located at the Daffodil Centre (Cancer Council NSW and University of Sydney) headed by Professor Anne Cust is involved in international melanoma consortia research programs including the Genetics of Melanoma (GenoMEL) consortium, the Genes, Environment and Melanoma (GEM) consortium, and the Integration of Clinical and Molecular Biomarkers for Melanoma Survival (InterMEL) consortium.
- *Cardiovascular disease:* Cambridge Baker Systems Genomic Initiative is a transnational research team with nodes at the Baker Institute (Melbourne) and the University of Cambridge (UK). The partnership brings together data science expertise and massive multi-

omics datasets and is also part of The Alan Turing Institute and Health Data Research UK. The focus is research questions in cardiovascular and respiratory disease.

- *Psychiatric conditions*: The international Psychiatric Genomics Consortium involves over 800 investigators from 36 countries working with data on more than 400,000 people. The Australian Genetics of Depression Study (~20,000 participants with depression) is the largest Australian study contributing to the consortium (137).

Australian professional associations

No position statements on any aspect of PGS have been published by professional associations in Australia. A range of professional associations will need to develop positions and guidelines on use of PGS given its potential applications across many specialties as well as general practice.

- The *Human Genetics Society of Australasia (HGSA)* is currently developing a position statement on the *Use of Polygenic Scores in Clinical Practice and Population Health*, which will be published in the coming months.
- The *Cardiac Society of Australia and New Zealand, the National Heart Foundation of Australia and the Australian CV Alliance's Joint National CV Implementation and Policy Roundtable Draft Report* (May 2022)[22] mentions PGS:
    - in Key Messages: "Support trials that test/evaluate the use of innovative screening tools, such as Calcium Scoring Technologies and **polygenic risk scores** for efficacy and equity implications".
    - In Primary Prevention Aim 1: "All Australians know and understand their absolute CV risk: Provide supporting evidence and implementation plan for pilot projects for the introduction of new technologies and tools e.g., **polygenic risk scores**, coronary artery calcium scores; undertake cost-benefit analysis and health economic modelling."

GWAS and PGS development studies

Although not the focus of this report, it is worth noting the significant contribution of Australian researchers to GWAS and SNP discovery for use in a variety of PGS, often in collaboration with international teams using Australian and international datasets. A 2019 analysis of *GWAS central*, a database which summarises data from all GWAS studies, reported 24 studies involving Australian researchers and/or genomic information of Australians. These include GWAS of cancers, endometriosis, stroke, glaucoma, diabetes, epilepsy, alcohol consumption, corneal thickness and multiple sclerosis.

Australian cohorts

There are some well-defined clinical cohorts and resources in Australia available for researchers, such as the Breast Cancer Family Registry and the Kathleen Cuningham Consortium Foundation for Research into Familial Breast Cancer (kConFab) cohorts, which have been used to develop a PGS for use in the familial cancer setting (138). Another example is the *Medical Genome Reference Bank*

[22] Cardiac Society of Australia and New Zealand, National Heart Foundation of Australia & Australian CV Alliance. See https://ozheart.org/programs-and-events/implementation-and-policy-roundtables/

(MGRB) (139) at the Garvan Institute, which has sequenced the genomes of about 4,000 healthy older adults from two existing cohorts: the 45 and Up Study (Sax Institute) and the ASPirin in Reducing Events in the Elderly (ASPREE) Study (Monash University). The MGRB is available for use by researchers from Australia and overseas.

PGS development

Some examples of Australian research involved in identifying SNPs or developing PGS related to various diseases are:

- *Familial breast/ovarian cancer:* The Variants in Practice (ViP study)[23] at the Peter MacCallum Familial Cancer Centre started in 2012 and is collaborating with research groups in Australia and around the world to identify SNPs in familial breast and ovarian cancer as well as moderate and high-risk gene changes. ViP is a member of the global breast cancer association consortium (BCAC, led by Cambridge University). Numerous publications have arisen from this study (available on the website).
- *Colorectal cancer:* Researchers at the University of Melbourne in collaboration with others in Australia and overseas have developed a PGS for colorectal cancer (78).
- *Melanoma:* Researchers at Monash University assessed the performance of a melanoma PGS using data from the ASPREE study (140).
- Glaucoma: A groups at Flinders University (SA) and others in Australia and overseas have developed a PGS for glaucoma susceptibility and progression (93). Flinders University in collaboration with other universities has applied to have the PGS patented[24].

Improving GWAS diversity

As discussed earlier for GWAS from around the world, most Australian GWAS data have been derived from studies of people of predominantly European ancestry. Responding to the need for future GWAS to include diverse ancestries to reflect our population, particularly Aboriginal and Torres Strait Islanders, researchers are now tackling the issues of diversity of GWAS data and transferability of PGS to non-European ancestry populations. For example, Professor Daniel MacArthur from the Garvan Institute is developing a resource of Australian genetic variation that better represents our ancestrally diverse community. The aim is to make population-scale genomic medicine more accessible and equitable in Australia and elsewhere.

Australian studies assessing clinical utility of PGS

The application of PGS in clinical practice is an area of active research in Australia, across several cancers and other diseases, particularly with respect to patient and health professional attitudes and understanding, risk communication, psychological and behavioural responses to receiving risk information and pilot implementation projects.

[23] See: https://www.petermac.org/research/familial-cancer/vip

[24] See: https://patents.justia.com/patent/20210118525

Large trials to inform population screening

The *Type 1 Diabetes National Screening Pilot*[25] is an implementation science research project investigating the feasibility, acceptability, and cost-effectiveness of three population screening models for **type 1 diabetes** in infants and children across five states (funded by the JDRF, Lead Investigator Dr Kirstine Bell, University of Sydney). Two arms involve a risk-stratified approach using a PGS (89) to identify children with an increased risk of type 1 diabetes. These children are then offered ongoing monitoring to detect early markers of pre-symptomatic disease. The study aims to recruit 9,000 children.

We did not identify any other large trials aiming to inform PGS in population-level screening.

Smaller trials and pilot implementation studies

Research teams in New South Wales and Queensland are conducting various studies into the effect of personalised genomic risk information on **melanoma** screening and preventive behaviours. A 12-month community-based RCT (n=1025) showed a reduction in the incidence of sunburn for those receiving PGS-based risk information compared to the control group, as well as increased skin examinations among women but not men (72). However, there was no effect on measured UV exposure. Importantly, those receiving low-risk results did not reduce their sun protection behaviours (72).

A study to assess the acceptability and feasibility of offering a PGS test for **colorectal cancer** in primary care (using the Australian-developed 45 SNP-based PGS (78)) was conducted at four general practices (n=150 participants aged 45-74 years) in Melbourne, Victoria (45, 82). After a short verbal explanation, the study showed a high uptake of the PGS test (84%) with nearly all participants showing good knowledge of the test (45). There was some suggestion of a positive impact on screening behaviour, but this will need to be tested further in a larger trial. An informed choice measure showed 73% made an informed choice (82). A subset of participants (n=16) was interviewed revealing a mostly positive attitude to the test (82). A subsequent RCT of this colorectal cancer PGS, the SCRIPT Trial[26], has recently completed recruitment of a cohort of patients (n~200) in general practice to determine the impact of risk-appropriate colorectal cancer screening. This research group has also examined the potential impact of risk prediction models (lifestyle model, genomic model and combined model) on theoretical population screening programs for colorectal cancer (83).

In related work by the same research group in Melbourne, work is commencing on a pre-trial study implementing a **multi-cancer PGS** in primary care to assess feasibility and acceptability, aiming to inform the design of future trials.

*The Early detection of **coronary artery disease** by polygenic and metabolic risk scoring (EDCAD-PMS) study,* at the Baker Heart and Diabetes Institute in Melbourne (and a site at the Menzies Institute in Tasmania) aims to identify whether a PGS can predict the presence of coronary calcium in the

[25] See: https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12622000381785p

[26] See: https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12621000092897

arteries and whether knowing the PGS or knowing the coronary calcium score (CCS) is more effective at reducing cardiovascular risk. Patients undergoing a PGS, metabolic risk score and CCS will be randomized to receive PGS or CCS information and followed to measure reduction of risk over 12 months. Recruitment of 40- to 70-year-old asymptomatic people is underway and will be completed in 2023.

A research group headed by Professor Gemma Figtree has been awarded a *NHMRC Partnership Program - Partnership for Precision Prevention in CAD (PPP-CAD)*[27] for a program of work implementing a PGS to identify early risk of **CAD**. The study will provide data on whether PGS risk will work in practice in heart health checks in primary care and will inform clinical guidelines and government policy.

The PRIMO (Using Polygenic Risk Modification to improve **breast cancer** prevention) study[28] is a national RCT led by Professor Paul James aiming to compare the current standard of care with a personalised assessment of the risk of breast and ovarian cancer that includes 'single gene' testing, family history, personal risk factors and PGS. Participants are women with no history of breast or ovarian cancer undergoing testing for known familial mutations in high or moderate risk genes. Outcomes include changes in risk behaviours and psychosocial impacts.

As part of a newly funded NMHRC Centre for Research Excellence on risk-based **breast cancer** screening, researchers in Victoria and WA are developing implementation studies in primary care that combine PGS with additional risk factors to tailor breast screening recommendations.

Understanding of PGS, behaviour change, public & professional views

Australian researchers are undertaking significant work in psychosocial aspects of **PGS in breast cancer,** particularly in the familial cancer clinic setting. A sub-study of the Variants in Practice (ViP) study is the *VIP Psychosocial aspects of genomic testing for breast cancer risk study*[29], which follows from an earlier pilot study. 400 participants of the ViP study were invited to receive their research PGS results – 200 with a personal history and 200 with a family history of breast cancer (141). Participants were surveyed before, 2 weeks after and 12 months after receiving their PGS result. At least 10 publications have already provided important information about uptake of the offer of a PGS result (142, 143), risk perception and understanding (46, 144-146), ways to communicate polygenic risk (147-149), and psychological and behavioural outcomes (142).

Other studies from the researchers who conducted the community trial of PGS in melanoma include a qualitative study of 30 participants from a pilot feasibility study (42) assessing attitudes towards offering genomic risk information for **melanoma and other common conditions** to the public (73), and a separate qualitative study with 22 general practitioners (GPs) evaluated GP attitudes to and expectations for providing personal genomic information (39), the results of which may help to inform implementation. A telephone communication protocol for disclosing **melanoma genomic risk** information to the public has been developed and evaluated (71). These researchers have also

[27] See: https://researchdata.edu.au/partnership-precision-prevention-ppp-cad/1780860

[28] See: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02240452/full

[29] See: https://www.petermac.org/research/familial-cancer/vip-psychosocial

authored a commentary on the potential for PGS and other risk information in precision prevention of melanoma and considerations for implementation (67).

A qualitative study has explored patients' (those with a diagnosis) experience and understanding of a PRS for **bipolar disorder** and found that most of those who received the PGS result found it acceptable and helped them understand their condition (44).

A survey of people with **glaucoma** on the Australian and New Zealand Registry of Advanced Glaucoma (n=1069) showed strong interest in a PGS for glaucoma had it been available before they were diagnosed (150). Those interested in the PGS test were more likely to recommend it to family members and to undergo testing for prognostic information (150).

Australian studies of attitudes of health professionals with respect to PGS suggest that despite expecting that they will be using PGS in future healthcare, knowledge and preparedness for discussing PGS with patients is low, with an expressed need for point-of-care resources and clinical guidelines to support implementation (39, 147, 151). Australian human research ethics committees could also benefit from resources (online and printed preferred) to help with assessing genomic research applications (152).

Health economic studies

Australian cost-effectiveness/benefit analyses are part of various research programs in PGS but have not yet been published, apart from the above-mentioned modelling of cost-effectiveness of a PGS for use in population-wide screening for primary open-angle glaucoma in Australia and the UK (129). Discrete choice experiments are a part of health economics that can inform implementation planning by eliciting patient preferences. A recent study of a discrete choice experiment for a PGS for cancer risk showed Australians prefer a PGS that is accurate, tests for multiple cancers, has non-invasive risk reduction measures, and is performed through primary care (153).

8. NATIONAL CONSULTATION

An essential part of the project was to consult widely with experts and others working in the field of PGS from a wide variety of backgrounds. Phase 1 of the consultation involved in-depth interviews with key informants. The findings from the interviews then informed a face-to-face stakeholder workshop (Phase 2) to explore the issues identified by the key informants and to find consensus on current gaps and priorities for future research.

8.1 Consultation process

Phase 1: Key informant interviews

Aim

To identify expert views of PGS in Australia around research priorities and requirements for translation into clinical practice.

Method

Based on current national and international PGS research and implementation, interview questions were devised by the Project Strategy Group. Four main areas were covered: current value in polygenic scores; usefulness of PGS in practice; barriers to implementation; and the tools and resources used in PGS. Interviewees were also asked for exemplars and future research models.

Semi-structured interviews (45 to 60 minutes long) were conducted by 3 researchers with experience in qualitative methods. Thirteen key stakeholders from Australia (n=11) and overseas (n=2) participated and interviews were recorded and transcribed. Participants included professionals from genetic medicine, health and bioethics, cardiovascular medicine, primary care (cancer), molecular pathology, statistical and computational genetics, policy, and genetic counselling. A consumer involved in patient advocacy was also interviewed.

Data analysis

The data were analysed for content and themes extracted to convey the main points of the discussions. All analysis was undertaken in line with the aim of developing research priority areas of strategic importance to Australia. A full report of the interview findings is provided in Appendix 3.

Phase 2: Stakeholder workshop

Aim

To consult with a wider group of experts for discussion and feedback on priorities with respect to PGS research areas and questions arising from the national and international landscape analyses and interviews (Phase 1 consultation), to identify gaps and areas of consensus.

Method

Data from the Australian and international landscape analysis and the key informant interviews were examined by the Project Strategy Group to devise a series of four possible priority research areas and research questions within each area (see Appendix 4). These were used as a basis for discussion by the wider group of experts involved in the stakeholder workshop.

Invitations were extended to 82 experts from around Australia to attend a 4-hour in-person workshop held in Sydney on 23 May 2022. From the invitees, 31 attended. Two facilitators managed the group discussion and collated the outcomes as well as a workshop administrator. Participants worked in five groups comprising 4 to 6 people. Each group was mixed with respect to expertise, area of research and level of involvement in PGS, ensuring a variety of perspectives were considered.

Session 1: After a short presentation describing the background to the Polygenic Score Incubator Project and the aims of the workshop, participants were asked to work with those seated at their table (comprising a mix of research areas and clinical expertise). Groups were asked to consider the priority research areas and the research questions (Appendix 4), keeping in mind the following questions:

- Do you agree with the priority research areas and questions (rewording or additions)?

- Can you prioritise the statements and/or questions?

A nominated spokesperson from each group gave feedback on the group's discussion.

Session 2: After a break, groups re-convened and were asked to consider the following:

- What type of studies would we recommend: clusters, small pilots, large exemplars (a wide call or specific)?
- What are the priority topics, conditions, concerns?
- What criteria should be used in prioritising possible exemplar areas for implementation research?

Again, a spokesperson from each group was tasked with summarising the group's discussion for the rest of the participants. Outcomes of the group discussions were presented on paper and post-it notes were added to record other points that arose as the broader discussion was taking place.

Data analysis

Following the workshop, notes from the group presentations were collated by the facilitators. The Project Working Group (n=4) extracted the main themes from the workshop notes and identified areas of agreement amongst participants. Through this process, the Working Group identified areas of consensus for PGS research and implementation, leading to a series of recommendations for future research.

8.2 National consultation findings

A summary of the main findings from the national consultation with respect to research gaps and priorities is given below.

The expertise and interests of the participants of the interviews (n=13) and workshop (n=31) covered a broad range of areas related to the PGS landscape in Australia, including GWAS; genomic diagnostic laboratory; statistical/computational genetics; cancer (breast, colorectal), diabetes, autoimmune, cardiovascular disease, glaucoma; the use of PGS as a diagnostic and stratification tool; PGS methodology and development of frameworks for clinical use and in academia; translation in primary care; ethical aspects of PGS; direct-to-consumer testing; resource development and education for clinicians and the public; and PGS and psychosocial/behavioural outcomes.

The value of PGS

The main theme from both phases of the consultation was that PGS will have clinical value (as suggested by current evidence), but presently it is primarily in the research realm and not yet ready for clinical practice. Moreover, demonstrating the clinical value (see Box 1, page 18) of PGS for a defined purpose in a specific context (see Box 2, page 19), over already existing risk information, is key to implementation.

The potential value of PGS was discussed in the context of tailored screening programs with health system resources directed to those at higher risk; using PGS to map to existing risk-based recommendations to tailor prevention strategies; identifying subgroups for early intervention; and reducing diagnostic odysseys. There was some discussion of the potential of personalised

information to impact on behaviour and the need to understand how PGS information will affect risk-reducing behaviours so that the theoretical benefits of PGS information are realised.

What do we need to know about PGS to facilitate implementation in Australia?

Table 3 below summarises the main themes related to needs for PGS research and implementation arising from both phases of the national consultation, and possible research questions participants suggested could help to advance the field of PGS in Australia.

Participants also recommended underlying considerations for PGS research and a summary of these are given below the table (Considerations for research).

Table 3: PGS themes identified in the national consultation and possible research questions

Theme	Possible research questions
Value of PGS – what is needed to show value?	
• Value has many meanings and is context dependent • Build the evidence base on how and where PGS adds value	• When and how do polygenic scores improve the outcomes of care for patients? For populations? • What added value do they have that is not already measured in a different way (e.g., existing risk tools)?
Clinical Utility – what is needed to demonstrate clinical utility?	
• Depends on test and changes over time • Purpose and context are important – e.g., clinical utility of PGS for identifying disease risk is different to PGS for aiding disease diagnosis or therapy • Cross-lab reproducibility of PGS • Evidence-based clinical guidelines • Impact of PGS result on intervention or treatment (PGS should be linked to an intervention) • Regulation of PGS – who/how to decide test has clinical utility • Best way to report PGS to clinician and patient: reporting standards and clinical resources needed • Demonstration of cost-effectiveness	• How can PGS work alongside current processes? • Who are the beneficiaries of tests? How do they differ for each test? • What constitutes a reasonable level of evidence for implementation? • Does PGS motivate health behaviour change or lead to a sense of genetic determinism? How do you encourage uptake of preventive measures? • Do people engage in the health system more and/or in more efficient ways?
Infrastructure – what is needed for implementation?	
• Tools – electronic assessment tools integrated with current systems and easy to use • Pipelines – continuity from lab to patient (bench to bedside) • Workforce – implications across clinical specialties, not just genetics; patient consent	• What is the optimal reporting structure from laboratories to clinicians/patients? • Do you need to offer pre-test counselling? What is the best way to develop scalable genetic counselling and provide for non-genetic clinicians?

- What infrastructure is needed to support the health workforce in a structured way (resources, people, coordination)?
- What infrastructure needs to be considered to support the public?
- How can we cross boundaries between health systems (e.g., electronic health records)?
- What are the health services/system consequences?

Ethical and legal implications – what needs to be considered?

- Data collection and storage guidelines/regulation
- Issues for PGS testing of children, eg., newborn screening for type 1 diabetes, children living with risk knowledge
- Inequity of access, especially for non-European populations (risk prediction models predominantly pertain to European populations) and specifically Aboriginal and Torres Strait Islander populations
- Understanding and managing different cultural understandings of PGS
- Private companies offering testing on user-pays basis
- How can we embed tools, tests, screening in an equitable manner? Need to engage culturally and linguistically diverse populations
- How do we address concerns around PGS, such as privacy, discrimination, stigma?
- How do we communicate shifts in policy?
- How could PGS affect insurance (need to educate insurers)?
- How can PGS for Aboriginal and Torres Strait Islander communities best be approached, from developing specific PGS tests from GWAS to clinical utility to community acceptance and education?
- Should PGS be used in prenatal (embryo) screening?

Understanding and education – how do we support clinicians and the public?

- Knowledge of public perceptions and understanding of PGS will inform education and communication strategies
- Education/resources for clinicians need to be developed
- Different groups in the community may have differing understanding and potential engagement with PGS
- How best to provide education on PGS to time-poor clinicians?
- How do people perceive and understand PGS risk?
- How do you best communicate risk results to patients? Does it need to vary by disease and context?
- How will patients understand and communicate family meaning of PGS?

Considerations for research

It was agreed that PGS research should cover the workflow pipeline, from GWAS studies and bioinformatics to uptake of health interventions following a PGS result, to health outcomes, and it should contribute to health and economic benefit.

Collaborative/multi-disciplinary research

- Research to date had been piecemeal and often occurred in silos; there is a need for collaborative research led or championed by a group of professionals, including a range of

specialities across academia and commercial/industry partners, with consumer stakeholders playing key roles.
- Monitor international landscape; build international collaborations and link in with international resources (e.g., UK Biobank)
- Consortia will be very valuable to avoid duplication of effort and guide research ('hub and spoke' a possible model to manage multi-disciplinary, multi-institution consortia)
- Health economists, implementation scientists, sociologists, anthropologists and healthcare professionals all important
- Link with existing screening programs to study PGS; use other existing resources.

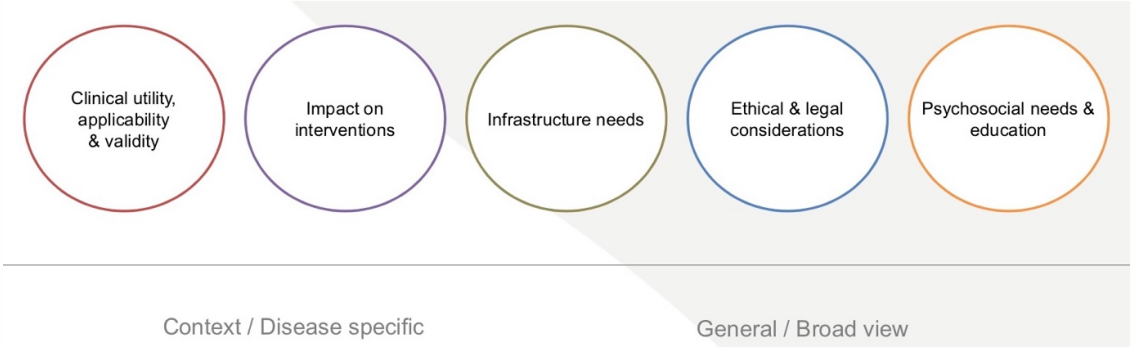
Context-specific PGS

- Some diseases, such as breast cancer, glaucoma and cardiovascular disease, are further progressed and likely to be translated first; PGS in psychiatry has potential in diagnostics and therapeutics
- Funding could be directed to support economic feasibility, health outcomes and cost-effectiveness to provide a 'proof of use' in these conditions
- Using one disease as an exemplar may provide model for PGS in other areas: 'high value' pilot studies (important condition, scalable)

Broader issues (applicable across contexts)

- Clinician and public/patient understanding, acceptability
- Use evidence from other areas, such as research in monogenic conditions; risk perception; risk communication; behaviour modification to reduce disease risk
- Workforce issues – practitioner roles and support; develop core competencies for various practitioners
- Communication and education needs
- Ethical and legal questions, such as collection and storage of data; access to data; use of PGS in reproduction, children
- A principle of equity of access to PGS needs to underpin all research to avoid exacerbating health inequities.
- Health technology assessment necessary for public funding and information needs should be a consideration in study designs
- Identification of future funding strategies for PGS implementation: funding for implementation, training, and consumer education will be required on top of funding the PGS tests.

Summary of research areas for PGS implementation



8.3 Consensus themes and recommendations for PGS research

Several major themes around the current status and future needs of PGS research in Australia had broad consensus amongst the participants of the national consultation (Table 4). These were linked to specific recommendations that participants generally agreed could help to advance the field of PGS research.

Table 4: Consensus themes and research recommendations

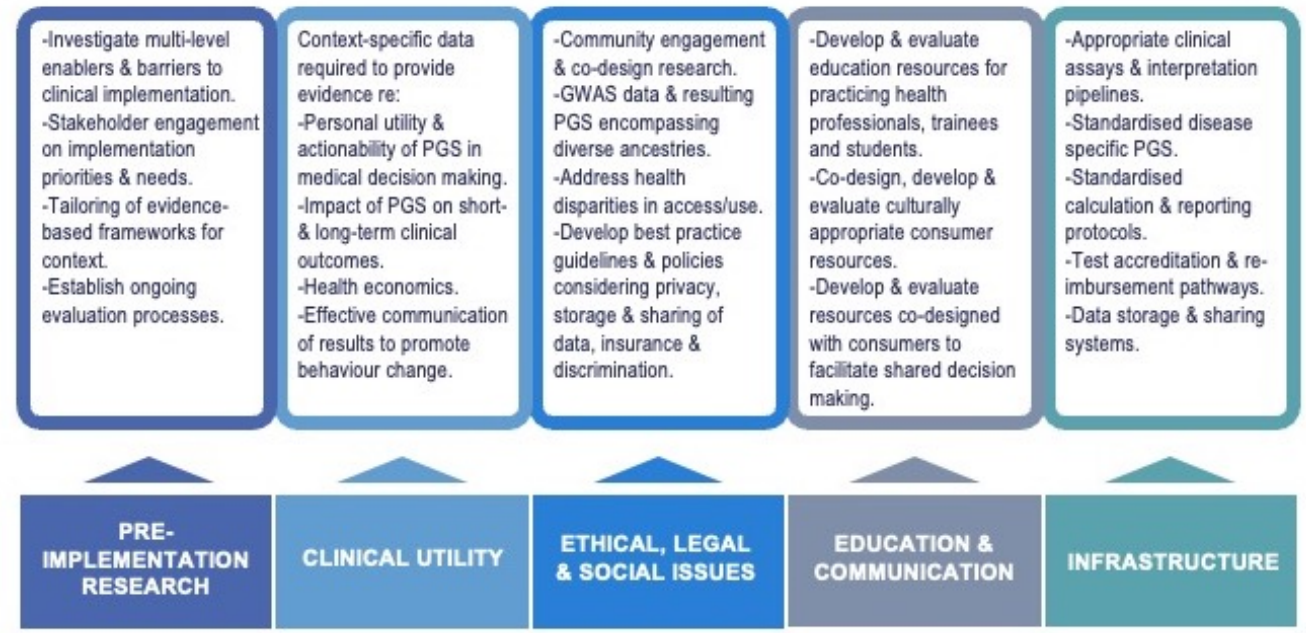
Consensus theme	Recommendation
Systematic collection of additional evidence is needed before clinical implementation, specifically with regards to demonstrating the value of PGS.	Collaborative groups around specific disease or condition areas should be tasked and resourced to curate information comparing performance and value of PGS guided by a set of common criteria.
Use of a PGS should have a clearly pre-defined purpose around risk prediction and management of health conditions with a clearly defined range of potential results, actions and consequences. It will not be used to assess traits such as intelligence or sporting ability.	Applications should only be considered for research relevant to the implementation of PGS into routine clinical practice where it can be demonstrated to influence decisions about clinical care including screening and relevant risk behaviour change.
Current PGS are not representative of the diverse Australian population and could exacerbate health inequities between groups of Australians.	• Investigate how to develop reference data that informs PGS for specific ethnic backgrounds. • Conduct a separate, specific consultation process with Aboriginal and Torres Strait Islander researchers and other community members to determine priorities for PGS research and implementation for Aboriginal and Torres Strait Islander peoples.
Collaborate, avoid duplication of effort and link to other research areas.	• Strongly encourage collaborations and/or consortia, both in Australia and internationally, to identify commonalities and build on existing knowledge, resources, and well curated datasets. • Alignment of future PGS studies with MRFF research priorities and partnerships should be considered. • Encourage partnerships with industry bodies (some of whom are already offering PGS tests).
It is difficult to prioritise one stream of PGS research over others.	• Concurrent research projects addressing questions from each research stream will be of benefit to overall advancement of PGS implementation knowledge.

Scalability of studies is an important consideration to facilitate timely implementation of research evidence into the Australian health system.	• Specific PGS contexts may be prioritised based on where they are along the research path: for example, breast cancer has good PGS tests, knowledge of risk communication, potential interventions, clinician knowledge, and some health economic evaluation, so it may be a candidate to demonstrate the full pipeline of the PGS patient journey. Other conditions may also be candidates for demonstration projects.

9. RESEARCH GAPS

The international and Australian landscape analyses and the national expert consultation show that despite a multitude of expert commentaries and a plethora of studies on many facets of PGS, from GWAS to clinical and public health application, there remain many gaps and challenges. The gaps identified in comprehensive expert commentaries (13, 17) were supported by our national consultation, albeit with a focus on Australian healthcare and health systems. Although studies demonstrating clinical utility of PGS in specific clinical contexts appear to be the most underdeveloped, there are gaps across the spectrum of implementation, as summarised in Figure 3. On the positive side, current and planned trials and other studies reviewed in the landscape analysis, both internationally and in Australia, will go some way to providing evidence for PGS implementation in the next few years.

Figure 3: Steps to implementation of PGS into public health and clinical care*



* We acknowledge the HGSA PGS working group for use of this figure.

10. RECOMMENDATIONS – PGS RESEARCH IN AUSTRALIA

Based on the data from landscape analyses and the national consultation, particularly the consensus themes and recommendations, the Project Working Group developed draft research recommendations and criteria for assessing research proposals. These were reviewed by the broader Project Strategy Group and feedback incorporated into the final recommendations. The Project Strategy Group approved the following recommendations for PGS research in Australia.

Each of the research streams in 10.1 are considered necessary for providing robust evidence to inform the implementation of PGS into the Australian health system for use in population health as well as individual clinical practice. As such, they are not weighted according to importance and do not suggest research silos.

Further, the streams of research are not meant to reflect funding streams; rather, the landscape analysis and expert consultation for this project **strongly underline the need for research to be conducted across streams, with collaboration between disciplines**. Therefore, for optimal outcomes, funding models will need to have the flexibility to incorporate cross-stream research proposals.

10.1 Streams of research

Stream 1: PGS assay and test development	Stream 2: Evaluation and implementation of PGS	Stream 3: Education, understanding, workforce issues
• Assays and tests, linked with purpose/context • Regulation of PGS tests – robust, effective, clinical assays and interpretation pipelines; Includes process for regulation around updating of PGS assays based on new SNPs/evidence • Consistent reporting (standards) of PGS results: from lab to clinician, from clinician to patient. This includes developing systems to record PGS data and metadata to facilitate transparent trace-back to track SNP weights used in any stored PGS	• Development of PGS clinical tools or integration of PGS into existing risk tools • Implementation of PGS clinical tools in practice: - Population level implementation studies, e.g., into existing screening programs - Primary care implementation - Specialist services • Frameworks tailored to facilitate evaluation of validity and utility of PGS • Evaluation at every point along PGS pipeline from laboratory to patient health outcomes • Health economic evaluation at every stage, from informing PGS implementation protocols (e.g., using discrete choice	• Education of clinicians and community education/health promotion • Social and ethical norms, such as community acceptance of PGS (e.g., is PGS seen as different to other non-genetic risk information?) • Insurance implications • Decision-making arising from a PGS result (e.g., preparedness to forego screening based on low-risk PGS) • Practitioner roles for conducting and reporting PGS tests (point of care: genetics health professionals, other specialists, primary care clinicians, direct to consumer testing)

	experiments) to cost-benefit analysis to inform governments/health systems and identify impact on budgets • Intervention and behaviour change studies, including long-term health outcome/behavioural follow-up studies • Health system requirements associated with PGS implementation, including electronic health records, data storage, data ownership and access • Health technology assessment • Possible funding strategies for PGS implementation

10.2 Guiding principles for Australian research

- **Value:** PGS implementation needs to add value (defined in Box 1) to the health system, individual patients, and/or public health. Current evidence suggests PGS information can be of value and research needs to demonstrate how and who it will benefit in the Australian context.
- **Context:**
    - Applications of PGS are context dependent (described in Box 2); however, there are some common elements to research and implementation.
    - Some contexts for use of PGS are further along the research path and may be more amenable to earlier implementation into the health system, serving as exemplars.
- **Equity:** Australian genomic reference data needs to represent the diverse genetic ancestry of the population, including Indigenous and other ethnicities, to ensure PGS research and implementation do not exacerbate health disparities. Equity of access to PGS for disadvantaged groups should be a consideration for implementation research, while acknowledging this is a broader systemic issue across the health system.
- **Collaboration:** Research must promote/demonstrate collaboration between researchers, clinicians, public health, and the community at all steps of the process and across disciplines.

10.3 Criteria for assessment of research proposals

Grant applicants demonstrating at least some of the following criteria should be given priority:

- A variety of research designs may be useful for PGS implementation research and researchers should demonstrate how their study design will provide robust and timely outcomes data. While RCTs are gold standard, hybrid designs or pragmatic trials may be necessary.

- Partnerships within the genomics and health research communities are a priority, to link into and build on research collaborations nationally and internationally; however, industry partnerships should be considered if they bring value to the study and competing interests have been assessed and managed.
- Use of existing suitable cohorts (sizeable and well-defined clinically) for developing and testing PGS tests/tools.
- Exemplar projects that can be implemented more widely if shown to have benefits for individuals' health and/or the health system (scalability).
- Projects that align with screening guidelines, if they exist, or use population screening programs to test PGS interventions (this will not be applicable to all disease areas).
- The health condition being investigated is important due to factors such as a high prevalence in the Australian community, a high heritability (genetic architecture), evidence that healthy behaviours are likely to be adopted based on PGS information, or other justification.
- Alignment with MRFF priorities and partnerships.
- Demonstration that the research will endeavour to produce equitable access and outcomes for the diverse Australian community. This could include consultation with groups such as the National Indigenous Genomics Consortium (led by Professor Alex Brown) to determine priorities for PGS research for Aboriginal and Torres Strait Islander people and to ensure culturally appropriate research practice.
- Clarity about the purpose of the PGS under investigation and the context in which it will be used, including the potential treatments, health outcomes, or behaviours that will be affected by the PGS test, where possible. In some contexts, the purpose of a PGS will be to enhance diagnostic, therapeutic or prognostic effectiveness or efficiency in clinical care.

10.4 Possible structures to support PGS research and implementation

A key theme from the consultation process (both in the interviews and the workshop) was that sharing of information/data sets across research groups in Australia and internationally will facilitate the optimal use of resources and minimise duplication. There are a variety of ways this can be facilitated, and many thought consortia, based either on a particular health condition or on a common interest in PGS, will be key to advancing translation into clinical practice.

In the near-term, most PGS-focused research will share key elements in terms of core technologies (e.g., genome-wide arrays, imputation), analytic approaches (e.g., thresholding or forms of penalised regression used to improve the selection of variants and weights) and milestones to the process of implementation (establishing utility and acceptability, exploring communication). It was noted in the consultation that centralisation of processes could help to reduce replication and to leverage experience, tools and data to achieve an optimal research environment in Australia. A potential model would be the formation of an Australian Common Disease Genomics Alliance, similar to the International Common Disease Alliance PGS Task Force, with a focus on PGS implementation, comprising experts in multiple disciplines working in the fields of PGS and/or common diseases. A consortium of this type would not aim to determine or direct the field but act as an identifiable forum for aggregating and exchanging expertise, advice and the development of collaborations, as well as a body to coordinate the sharing of data. Australian Genomics, as the national organisation for supporting the translation of genomics research into practice, could facilitate such an alliance with dedicated funding.

11. CONCLUSIONS

The use of genomic information in precision medicine and public health is a rapidly changing field with much promise for improvements in health through prevention and better and earlier treatment of disease. As the costs of genomic analysis to produce the data for PGS are relatively low and getting lower, and the diseases for which PGS have been developed are common in the population, there is great potential for widespread application or PGS in healthcare, but the field is as yet untapped in practice.

The major theme arising from all stages of this project is that the use of PGS in a range of healthcare applications for common complex diseases will happen at some point in the not-too-distant future, with potential to enhance disease risk prediction, improve diagnosis and prognosis, and aid treatment decisions and choice of therapeutic interventions. However, despite increasing activity from multiple groups, networks and individuals across all areas of PGS research, from basic GWAS to implementation trials, widespread use of PGS in healthcare systems has not happened anywhere in the world as yet, and a range of challenges will need to be addressed before it does.

An important and encouraging finding from this project is that in Australia, we have the tools for best practice, such as GWAS including diverse ancestries (research is currently underway), a strong publicly funded health system, good population screening programs, mechanisms for HTA and other regulatory processes, and a strong research and clinical community with the expertise and interest to produce the evidence necessary to inform responsible, fair and clinically effective PGS implementation. Existing collaborations between researchers within Australia and with international groups also suggest we are in a good position to make use of available resources and to make a significant contribution to the international PGS landscape. However, a strong message from the national consultation was that despite some collaborations, research is currently too “siloed” and systems to facilitate collaboration across research types and diseases and to enable shared resources would support efficient and timely research to feed into implementation planning.

There are challenges that are impeding clinical implementation of PGS into healthcare in Australia (and elsewhere), described in section 6. Foremost amongst these is to demonstrate clinical utility of PGS in specific use cases, including cost-benefit analyses. For example, the behavioural impacts of receiving a PGS are not well understood and yet this information is crucial to demonstrate benefit. Will those found to be at lower risk be willing to undergo less frequent or different types of screening tests and is this ethical? This is a fundamental question for PGS risk-stratified screening. Does a PGS test result motivate behaviour change beyond current risk predictions for someone at higher risk of heart disease (for example) or might it make them have a more fatalistic belief in the inevitability of disease given PGS is genetic information? Can we incorporate PGS into healthcare while not detracting from the broader social determinants of health?

Other areas we need to consider are those at the health system level, such as regulation and accreditation, systems for PGS testing and reporting, data storage and access, as well as individual health professional and patient level needs, such as education and information provision,

particularly resources and tools to support primary care practice. Many of these areas are already under investigation, but more work is needed.

When developing PGS research recommendations for this report, it became clear that research across the streams (1. PGS assay and test development; 2. evaluation and implementation of PGS; 3. education, understanding, workforce issues) is necessary and one type of research cannot be prioritised over another. In fact, programs of research across the streams, perhaps a demonstration project showing how PGS in specific clinical contexts/diseases could be developed from the test right through to the education and clinical support, with corresponding health economic evaluation. This would provide robust evidence for implementation that might also be translated to other clinical contexts or diseases. Some broad programs of research are already underway, but more are needed and given the rapidly developing field of PGS, research designs that provide timely research outcomes are imperative. Some diseases may be more amenable to demonstration or pilot implementation projects for risk-stratified screening and prevention in the immediate term, including breast cancer, CAD, colorectal cancer, melanoma and glaucoma. Other health areas have more potential with respect to diagnosis and therapeutic interventions, such as psychiatry.

The widely discussed lack of diversity in GWAS used to develop PGS is currently being addressed in Australian studies designed to better reflect the diverse ancestries in the Australian community and improve methods for PGS calculation for diverse ancestries. This could go some way to ensuring equity of access for people of non-European ancestry. The broader issue of access to PGS by groups in the community that already have lower access to, and uptake of, health services is beyond the reach of PGS research and may need to be tackled in a wider research call. However, the costs of PGS tests and public understanding and education, which both impact on equity of access, need to be at the centre of PGS implementation models.

Polygenic scoring is currently growing in scope and complexity and its adoption in health care is already happening, albeit in a piecemeal way. The objectives of the research priorities identified here are to ensure that use of PGS adds value to individual and population health; that the benefits are available equitably while minimising the risks of harm; that the clinical and general community understand its strengths and weaknesses; and where it is publicly funded that the community is assured that there is value in this public expenditure. The focus is on ensuring that systems are in place to facilitate ease of use in clinical care, minimising unnecessary duplication in testing while ensuring that the information is based on current best practice (including in algorithms), and is readily available at the point of decision making while maintaining appropriate confidentiality and security of stored information.

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Expert consultants

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- Professor Mike Inouye, University of Cambridge, UK – for contribution as an international expert
- Dr Sowmiya Moorthie, PHG Foundation, UK – for contribution as an international expert
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APPENDIX 1: INTERNATIONAL STUDIES OF PGS AND BREAST CANCER

Table A1: Current international breast cancer studies evaluating PGS in risk prediction models

Study name	Description	Current status
MyPeBS study (Europe) My Personalized Breast Screening study – https://www.mypebs.eu	A European Commission-funded randomized clinical trial aiming to evaluate a new breast cancer screening strategy by comparing a personalised risk-based screening strategy (based on clinical risk scores and polymorphisms) to standard screening among 85,000 women aged 40 to 70 years in 6 countries: Belgium, France, Israel, Italy, UK and Spain. Started in 2019, the study will finish in 2025, with follow-up data collected for 15 years from study entry for evaluation of long-term cumulative breast cancer incidence and breast cancer-specific survival. The study also includes online questionnaires completed by participants at baseline, 3 months, 1 year and 4 years after recruitment, and qualitative interviews with women in the intervention arm, to examine the ethical, psychological and socio-economic impacts of personalised risk screening for breast cancer (110).	Recruiting (33,195 women recruited 13 Aug 2022)
GENRE2 study (USA) The GENetic Risk Estimation of Breast Cancer Prior to Decisions on Preventive Therapy Uptake, Risk Reducing Surgery or Intensive Imaging Surveillance study – https://clinicaltrials.gov/ct2/show/NCT04474834	A US observational prospective study to determine if the addition of an individual PGS to the Breast Cancer Risk Assessment Tool (BCRAT) or Tyrer-Cuzick (IBIS) score will help women at **high risk** of breast cancer (aged 35 to 75 years) to decide to take (or not take) medication to prevent breast cancer. The baseline breast cancer risk reduction consultation including the PGS will be followed by annual surveys over 10 years to determine if and how the availability of the PGS influenced patient decisions regarding preventive medicine and medication compliance. A previous smaller study by the same group (n=151 women) showed that addition of a PGS to breast cancer risk estimates for women at increased risk of breast cancer influenced	Enrolling women from several Mayo Clinic sites. Target sample size = 900.

	women's intent to take, and actual uptake of, preventive endocrine therapy (116).	
BREATHE study (Singapore) BREAst screening Tailored for HEr (BREATHE) study – https://blog.nus.edu.sg/breathe	A Singapore prospective cohort study to assess acceptability and potential changes in screening behaviour using a comprehensive risk-based personalised breast screening strategy (111). BREATHE integrates genetic and non-genetic breast cancer risk prediction tools to personalise screening recommendations and aims to recruit about 3,500 women aged 35 to 59 years from 4 sites. The study will also include a cost-utility analysis (111).	Recruiting since October 2021
WISDOM study (USA) Women Informed to Screen Depending On Measures of risk study – https://www.thewisdomstudy.org	Funded by the Patient Centered Outcomes Research Institute (USA), WISDOM is a pragmatic, adaptive, randomized clinical trial comparing a comprehensive risk-based, personalized approach (including PRS with other genetic and non-genetic risk factors) to traditional annual breast cancer screening in women aged 40 to 74 years. The multicentre trial aims to enrol 100,000 women, powered for a primary endpoint of non-inferiority with respect to the number of late-stage cancers detected. The trial will determine whether screening based on personalised risk is as safe, leads to less morbidity, is preferred by women, will facilitate prevention for those most likely to benefit, and adapt as we learn who is at risk for what kind of cancer (112).	Recruiting (49,447 women recruited by 13 Aug 2022)
BC-Predict (UK) Risk model added to the UK NHS Breast Screening Program (NHSBSP) – https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-to-include-assessment-of-breast-cancer-risk-in-breast-cancer-screening-bc-predict	A non-randomised fully counterbalanced study design to include approximately equal numbers of women offered NHSBSP (n = 18,700) and BC-Predict (n = 18,700) from selected screening sites in the UK (n = 7) (113). BC-Predict collects information on risk factors (self-reported family history and hormone-related factors via questionnaire; mammographic density; and in a sub-sample of approximately 1000 women, SNPs). BC-Predict produces risk feedback letters, inviting women at high risk (≥8% 10-year) or moderate risk (≥5 to < 8% 10-year) to have discussion of prevention and early detection options at Family History, Risk and Prevention Clinics. Outcomes include uptake of risk consultations, chemoprevention and additional screening as well as possible harms such as increased	Recruitment completed.

	anxiety. A decision-analytic model-based cost-effectiveness analysis will identify the key uncertainties underpinning the relative cost-effectiveness of embedding BC-Predict into the NHSBSP.	
DECIDO study (Spain) Personalised breast cancer screening in the Spanish National Health Service – https://clinicaltrials.gov/ct2/show/NCT03791008	The objective of the DECIDO study is to assess the acceptability and feasibility of offering risk-based personalised breast cancer screening and its integration in regular clinical practice in a National Health System setting (114). It is a single-arm proof-of-concept trial. The aim was for a study sample of 385 women aged 40–50 years resident in a primary care health area in Spain. The risk model includes a PRS using 83 SNPs.	Recruitment completed (December 2021)
PERSPECTIVE I&I study (Canada) Personalized Risk Assessment for Prevention and Early Detection of Breast Cancer: Integration and Implementation study – https://genomecanada.ca/project/personalized-risk-assessment-prevention-and-early-detection-breast-cancer-integration-and/	The PERSPECTIVE I&I project has 4 activities undertaken largely in parallel: 1: Identification and validation of novel moderate-to-high-risk breast cancer susceptibility genes through a well-powered whole exome sequencing (WES) case-control study, in order to develop a more comprehensive multi-gene panel test. 2: Improvement, validation and adaptation of a comprehensive risk prediction web-tool suitable to the Canadian context. 3: Development and piloting of a socio-ethical framework to support implementation of a personalized risk-based approach to breast cancer screening at the population level. 4: Economic analysis to optimize personalized risk-based screening implementation (115).	Recruiting women aged 40-69 years.

APPENDIX 2: NHMRC & MRFF GRANTS RELATED TO PGS

Table A2: Examples of NHMRC grants (2019 to 2021) including PGS as part of the project/program

Lead investigator	Institution	Title of study or program of research
Dr Puya Gharahkhani (2019)	QIMR Berghofer Medical Research Institute	Identifying the contribution of phenotypic and genetic risk factors for complex traits, with implication to risk prediction and causal inference
Prof Naomi Wray (2019)	University of Queensland	Quantitative genomics of common disease
Prof Grant Montgomery (2019)	University of Queensland	Improved clinical outcomes from understanding risk factors for reproductive diseases
Dr Jian Zeng (2019)	University of Queensland	Statistical methods and tools to integrate genetic and non-genetic data for risk prediction of common diseases
A/Pr Daniel Buchanan (2020)	University of Melbourne	Precision prevention of colorectal cancer: understanding tumorigenesis in high-risk people to optimise prevention
Kunal Verma (2020)	Baker Heart and Diabetes Institute	Early detection of coronary artery disease: An opportunity to start secondary prevention without a coronary event
Dr Anna Calkin (2020)	Baker Heart and Diabetes Institute	An integrative approach to define and attenuate genomic risk of coronary artery disease
Prof Gemma Figtree (2021)	University of Sydney	Partnership for Precision Prevention in CAD (PPP-CAD)
Dr Tatiane Yanes (2021)	University of Queensland	Personalised melanoma risk score: Development and evaluation of a co-designed toolkit for nation-wide implementation
Prof Melissa Southey (2021)	Monash University	National precision health research translation for breast and prostate cancer prevention and early detection
Assoc Prof Brian Drew (2021)	Baker Heart and Diabetes Institute	Polygenic mitochondrial dysfunction in heart failure and neurodegeneration

Note: we could not identify any 2022 NHMRC grants as having a PGS component

Table A3: Examples of MRFF grants (2017 to 2021) including PGS as part of the project/program

Lead investigator	Institution	Title of study or program of research
Professor H. Peter Soyer (2017)	University of Queensland	Personalised early detection of melanoma
Professor Anne Cust (2020)	University of Sydney	Genomic risk prediction and risk-tailored screening and early detection for common cancers
Professor Gemma Figtree (2021)	University of Sydney	New frontiers in personalised prevention of coronary artery disease

APPENDIX 3: KEY INFORMANT INTERVIEWS – FULL REPORT

1. Background

The application of genomic technologies in health is expanding including understanding the genetic contribution to common complex disorders. The application of polygenic risk scores (PRS) can contribute to risk stratification including the likelihood of developing common complex diseases (for example: cardiovascular disease, cancer and diabetes).

Given the burden these common and complex diseases place on the health system, the use of polygenic risk scores to identify high risk subgroups of the population is emerging as a research priority area and has started to attract funding investment internationally.

However, from a public health perspective, complex genetic risk prediction algorithms are rarely carried through to health system implementation at this time, and there remains the challenge of incorporating environmental factors (socioeconomic, access to care, behaviours, etc) in population health risk prediction. Further, there is a need for PRS to be applicable across different ethnic groups to deliver benefits equitably.

The aim of the working group is to develop health genomic research priority areas that are of strategic importance to Australia. These priority areas will be identified through parallel processes: (a) landscape and literature review and (b) interviews with key stakeholders. The content of this report refers to process (b).

2. Interviews

2.1 Methods

Interviews were conducted with domain experts across several fields to ascertain: perceived value of PRS; barriers to implementation into the health system and potential gaps to inform research directions. Interviews were conducted by three researchers with experience in qualitative methods and each interview went for approximately 45 minutes. All interviews were recorded and transcribed. The data was analysed for content and themes extracted to convey the sentiment of the conversations. All analysis was undertaken in line with the goal to develop health genomic research priority areas of strategic importance to Australia.

2.2 Participant details

Participants (n=13) were interviewed from across Australia and internationally and included professionals from: genetic medicine; health and bioethics; cardiovascular medicine; primary care (cancer); molecular pathology; statistical and computational genetics; policy; and genetic counselling. A consumer involved in patient advocacy was also interviewed.

Professionals had a broad scope of expertise and areas of interest. These included:

- Association and GWAS studies

- Cancer (breast, colorectal), diabetes, autoimmune and cardiovascular disease, glaucoma; the use of PRS as a diagnostic and stratification tool; and targeted screening and prevention
- Clinical translation in primary care
- Statistical and computational genetics
- PRS methodology and development of frameworks for clinical use and in academia
- Applications of genetic and genomic technologies
- Ethical aspects of PRS use
- Direct to consumer genetic testing or online DNA testing
- Resource and tool development for clinicians
- Training and education for clinicians and the broader public
- PRS and psychosocial and behavioural outcomes.

3. Results

3.1 Value of PRS

Most informants perceived the current value of PRS to be primarily confined to the research space. Although it was noted that cancer, glaucoma, and cardiovascular disease were more advanced, all informants spoke of the future *potential value* of PRS.

Generally, PRS was described in terms of *"another piece of the puzzle to contextualise risk"* and stratify populations. However, value was seen as context dependent. For example, in cancer (discussed mainly in the context of breast cancer), PRS was seen to have *"reasonable data around their clinical validity in terms of improving risk discrimination"* to impact risk mitigation strategies and explain some of the variability in families. Incorporation of PRS in cardiovascular disease alongside conventional risk factors was seen as *"just a way of identifying risk that effectively we don't understand fully…there's obviously the mechanistic insights that we may get by going back to the bench and trying to understand each of the variants that are strongly or weakly associated. But in the meantime, we should make the most of the valuable information"*. In glaucoma PRS was said to provide a more sensitive risk assessment as *"probably more than 99% of glaucoma patients don't have mutations there [identified gene] ... they can do genetic testing there, that's not the most common, so that's where the PR comes in. It's applicable to everyone, and that's probably analogous to the situation in with, for example, BRCA gene and breast cancer and ovarian cancer"*. Advances in the use of PRS for skin cancer risk in organ transplant patients was also highlighted as a niche, but effective, use of information to stratify risk. PRS as part of the diagnostic pathway was also noted for coeliac disease and newborn screening of Type 1 diabetes.

The potential value of PRS was linked to tailored screening programmes and targeting health system resources to those at higher risk; using PRS to map to existing risk-based recommendations to tailor prevention strategies; identifying subgroups for early intervention and/or reducing diagnostic odysseys. Some informants spoke of the potential of personalised information to impact on behaviour.

3.2 Barriers to implementation of PRS and research foci

3.2.1 Clinical Utility

Most key informants noted the challenge for PRS was to demonstrate clinical applicability and utility and to have defined additive value.

"We don't yet have a really good sense of what polygenic scores can do over and above what existing interventions can do…it's not to say that they won't have any value, but I would say let's work out what that benefit might be before we implement."

The value-add and validity would need to be disease-specific and across populations. Some noted that for clinicians to incorporate PRS into practice there will need to be a strong evidence-base for (a) how and where it may help with clinical management and/or (b) how it may affect behaviour change; but *"it's really going to be just about the extent to which it's seeing perceived to be clinically useful*." It was recognised that, for most diseases, work was still ongoing on positive predictive values and utility; and that as new genes are discovered *"then your PRS of yesterday now becomes obsolete."* Others noted that some conditions where PRS may be useful are still not well characterised.

Several outlined the need for clinical guidelines but were unsure what would constitute a reasonable level of evidence for implementation.

Barriers regarding the assessment of clinical benefit for patients and the need to link to recommendations for prevention and treatments were also noted by many, which led to questions about patient management for those with higher risks, or those who may develop conditions but are outside of the upper risk limits. *"You know you may get a PRS that shows your patient is in the top, has an increased risk for say, heart disease or breast cancer or something, but then what do you actually do with it?"* Some informants were also unsure where PRS would fit within the clinical space where a range of genetic tests are available for, for example, moderate risk genes.

"I think those are some of the uncertainties that still need to be worked out... where in the healthcare system? PRS is a loner or [you do] PRS plus other random genetic tests to make sure that you're not falsely reassuring people that they're at low risk but actually they just happen to have a moderate risk that you haven't tested at all."

Most pointed to the need for clinical education and resources, especially around the practicalities of ordering and interpreting tests.

- When and how do polygenic scores improve the outcomes of care for patients? For populations?
- What is the value-add of PRS to existing interventions? What do they offer that is not already measured in a different way? What can they add to improve health outcomes?
- How can PRS work alongside current processes?
- How will PRS scores be regulated. Who decides that a test has clinical utility?
- How are PRS scored linked with current interventions and how can impacts on morbidity, mortality, health and economics be measured?

- What are the positive and negative impacts of PRS tests?
- Who are the beneficiaries of tests? How do they differ for each test?

The point was also raised that, except for a few diseases, PRS is only useful in risk stratification and are limited by disease heritability. As such, any increases in predictive ability will be small-modest; *"there's not going to be any game changes in this because most people who get sick are not going to be your high PRS, the distribution practically states this…there's just more individuals in the bottom bit of the distribution"* although this may change as the GWAS grows. Some informants thus raised the issue of evidence thresholds for implementation and acceptable trade-offs between predictive ability and minor inaccuracies in risk prediction.

- What constitutes a reasonable level of evidence for implementation?
- What is an acceptable trade-off between small increments in prediction and potential to provide small inaccuracies? Is more modelling needed?
- What evidence level does a test need to meet to trigger funding or scalability?

How and what should be reported was also raised, with informants questioning the pros and cons of percentile versus absolute risk scores.

More widely in discussions of clinical utility, most noted that there was a need to demonstrate the cost-effectiveness of PRS.

Further, many of the informants felt strongly that PRS should be linked to interventions. Barriers related to behaviour change models per se were raised in relation to PRS specifically; with a need to understand what interventions work, with whom and under what circumstances. Several were not aware of interventions that were available for PRS. Most expressed uncertainty that PRS would motivate behaviour change (especially for risks that were a long way into the future); alternatively, a few suggested that PRS may encourage a sense of fatalism and diminish personal responsibility, and therefore behaviour change.

- Does PRS motivate health behaviour change or lead to a sense of genetic determinism?
- Will PRS influence behaviour positively?
- How do you encourage uptake of preventative measures?
- What is the uptake of interventions? What is the compliance and utility? How does PRS affect compliance above and beyond knowing your family history for example?
- Do people engage in the health system more and/or in more efficient ways?
- Who would benefit in certain therapies or behaviour change interventions?

3.2.2 Infrastructure

Infrastructure barriers to implementation included:

- Tools – the need for electronic assessment tools that integrated with current systems and were not too laborious to input
- Pipelines – from the need for continuity between labs in testing and interpretation to pathways to MBS and PBS, and
- Workforce implications – barriers were noted with obtaining consent from patients (time and a need to ensure they are informed). There was also uncertainty about how PRS should

be pitched as "PRS tests are not like a genetic test. It's not like you've got a BRCA mutation and therefore your children will get breast cancer. It's not like that, and so the implications in terms of genetic counselling are not the same". One informant suggested a move towards context-dependent technological advances in patient resources, especially if PRS is used for screening as this would exclude the availability of genetic counsellors to be involved. Further, as PRS can change over time and be re-evaluated as new information is developed "do we have capacity for that across all levels... do genetic services have a capacity to be seeing everybody every five to 10 years and then the GPs? How are we going to provide this in practice?"

- Do you need to offer pre-test counselling?
- What infrastructure is needed to support the health workforce in a structured way (resources, people, coordination)?
- What infrastructure needs to be considered to support the public?

3.2.3 Ethical and legal implications

"Just because we can do something doesn't mean we should" and several informants noted the need to consider the ethical implications of PRS now and what may arise in 3, 5, or 10 years' time. A couple raised the issue of data collection; when and where is data collected and by whom? In terms of newborn screening, although a convenient data collection point, informants raised several ethical issues concerning consent and loss of autonomy. In relation newborn screening of Type 1 diabetes, the following possible research questions were raised:

- Does early identification of type 1 diabetes result in earlier intervention? Better outcomes?
- Is there acceptability of this type of screening amongst parents? What are their preferences for return of findings? (only those where we can intervene?)
- What is the effect on the parent-child bond? That is, parents will only know their child as an at-risk person.
- Could newborn screening be used to investigate population level burden, changes and where resources may be needed (as opposed to individual level PRS)?
- How will it impact children living at 'high-risk'?

All informants raised the issue of inequality in risk prediction models for non-Caucasian populations, noting that PRS references databases are not ethnically diverse. This has the potential to further the heath care divide and broaden the gap and therefore more work needs to be invested to ensure equitable, accurate applicability across different populations. Further, research exploring how different populations understand genomic testing in the context of their own culture would help to overcome culturally specific barriers.

Ethical considerations were also raised with the use of PRS into inform risk-based screening, not only in terms of broader population acceptability but also in the potential for an elective user-pays system that would exclude lower SES populations. Diversity, equity and access need to be investigated.

- CALD populations need to be engaged to ensure the translation of information into plain language statements and literacy levels that work for individuals, groups.
- How can we embed tools, tests, screening in an equitable manner?

- What is the best way to communicate shifts in policy around population vs stratified screening?
- What is the level of acceptability for this?
- How do we address concerns around PRS, such as privacy, discrimination, stigma?

The impact of PRS on insurance was also raised, with informants questioning the ability of companies to understand the nuances involved and a need to ensure this information is used appropriately.

3.2.4 Understanding and education

Research investigating the public's perception and understanding of PRS was deemed important to help inform education, resources and communication strategies; which may be important influencers for positive behaviour change.

Broader conversations with the public and different publics are important to uncover how groups may engage with PRS in different ways.

- How do people perceive and understand PRS risk?
- What do people understand when they receive PRS, what does it mean to them, how much weight do they give to PRS?
- How does reported versus tested ancestry affect people?
- Psychosocial research around family meaning and communication of PRS.
- How do you communicate results to patients? Does it need to vary by disease and context?

3.3 Considerations for future research

Many informants noted that research priorities needed to align with unmet needs and should traverse the workflow pipeline. One suggested embedding clinical trial designs in primary care as a way to dynamically develop guidelines. Overall, informants endorsed research directions that contributed to the reduction of health costs and improved patient outcomes.

Several informants commented that research to date had been piecemeal and often occurred in silos. Therefore, research needed to be collaborative and led or championed by a group of professionals. Most called for research teams to include a range of specialities across academia and commercial/industry partners with consumer stakeholders playing key roles. Health economists were thought to be of highest priority, with others noting the need to also include implementation scientists, sociologists, anthropologists as well as healthcare professionals.

Informants also suggested that research questions and directions were context specific. Some diseases, such as breast cancer, glaucoma and cardiovascular disease, were further progressed in the PRS space and were likely to be translated first. Therefore, funding could be directed to support economic feasibility, health outcomes and cost-effectiveness to provide a 'proof of use' to further gains in reimbursement/payment conversations (MBS/PBS). One informant stated that using one disease as an exemplar may provide impetus to further PRS in other spaces.

The other focus on potential research questions and directions were more general and focussed on clinician and public/patient understanding, acceptability, communication and education needs and ethical and legal questions.

APPENDIX 4: PRS PRIORITY RESEARCH QUESTIONS FOR HEALTH SYSTEM CONSIDERATION

1. **PRS Testing Value**
   That research be conducted into the value of polygenic scores for improving outcomes of care to understand:

   a. The clinical endpoints, other benefits, and cost-effectiveness for individuals and populations.
   b. The limitations and unintended consequences.
   c. The experience of practitioners and patients of the additional information from PS testing on decision-making?

2. **PRS Testing and Test Result Characteristics**
   That research be conducted into what is required with PS Testing to:

   a. Ensure reproducibility of the genetic data used to construct a PS in everyday health care practice?
   b. Ensure reproducibility of the risks scores calculated from the same genetic data?
   c. Ensure the most appropriate storage of PS information including allowing the PS version of PS held in a health or research record to be tracked across time and different clinical locations, including who can access and in what circumstances
   d. Identify steps needed for a PS test to become an algorithm applied to existing genetic data as opposed to being disease-specific tests that generate genetic data.

3. **PRS Testing Implementation (Practicalities)**
   That research be conducted into the best service models for use of tests including:

   a. The ordering of tests including consent, context and professional role.
   b. The use, reporting and communication of results to practitioners and individuals?
   c. Whether/how test providers should be limited?
   d. The requirements for ongoing testing of genetic sequence or assays.
   e. The social and ethical issues relevant to PS in the Australian context.
   f. Equitable models of funding for PS?

4. **PRS Testing Education**
   That research be conducted into the education requirements of practitioners and the community to understand:

   a. The most appropriate models of education at tertiary and practitioner development level.
   b. Effective models of community engagement and education
   c. The practitioner and community requirements for informed decision-making?