Research priorities for Australian pharmacogenomics

Final report from the Pharmacogenomics Incubator Project working group

August 2022

Australian Genomics

FOREWORD

This work was commissioned by Australian Genomics to scope out the role of pharmacogenomics in clinical care and to identify opportunities for impactful research. A strategy group of experts was formed to guide a national consultation of stakeholders and an international landscape analysis. The following report lays out the process and findings, and the key recommendations for Australia.

PROJECT TEAM

Leads

Professor Robyn Ward and Professor Andrew McLachlan

Coordinator and lead author

Dr Stephen Hughes

Working group

- Professor Robyn Ward, Executive Dean and Pro Vice-Chancellor Medicine and Health, Faculty of Medicine and Health University of Sydney
- Professor Andrew McLachlan, Head of School and Dean, Sydney Pharmacy School University of Sydney
- Dr Stephen Hughes, University of Sydney
- Amali Disanayaka, Research Support/Coordinator, Australian Genomics

Strategy group members

- Professor Robyn Ward
- Professor Andrew McLachlan
- Professor Carl Kirkpatrick, Centre for Medicine Use and Safety, Monash University
- Sarah Steinke, Metro North Health & University of Queensland
- Dr Stephen Hughes
- Amali Disanayaka

DEFINITIONS

Precision medicine	A broad term used to describe applying genes, environment and lifestyle information and clinical data to guide health related decisions.
Analytical validity	A measure of assay performance, the sensitivity and specificity of the test to detect the genetic variant of interest.
Clinical validity	A measure of the ability of the test to predict the clinical disorder or phenotype that is associated with that gene or genotype i.e. the response of the drug in the individual.
Clinical effectiveness	A measure of the clinical outcome of the test (a demonstration that it is better than an alternative or usual care).
Clinical utility	A measure of the usefulness of a test, its influence on clinical decision making and outcomes important to individuals and family (sometimes viewed as a combination of effectiveness and cost effectiveness yet should be considered a third concept).
Cost effectiveness	A measure of the costs of testing against resultant cost savings (a demonstration it is better than an alternative or usual care).

ABBREVIATIONS USED IN THIS REPORT

CPIC	Clinical Pharmacogenetics Implementation Consortium
DPWG	Dutch Pharmacogenetic Working Group
PharmGKB	Pharmacogenomics Knowledge Base
PharmVar	Pharmacogene Variation Consortium
HLA	Human leucocyte antigen
DPYD	Dihydropyrimidine dehydrogenase
PK	Pharmacokinetics
PD	Pharmacodynamics
CDS	Clinical decision support
EHR/EMR	Electronic health(medical) record
TGA	Therapeutic Goods Administration
MBS	Medical Benefits Scheme
PBS	Pharmaceutical Benefits Scheme
NATA	National Association of Testing Authorities
U-PGx	Ubiquitous Pharmacogenomics Consortium
US FDA	United States Federal Drug Administration
EMA	European Medicine Agency
NHS	National Health System

CONTENTS

EXECUTIVE SUMMARY

The impact of adverse drug reactions (ADR) on health care is significant. In Australia, medication-related problems cost the health system $1.4 billion and are the cause of 250,000 hospital admissions annually. It is assessed that half of medication-related harm is preventable. Medicine safety in Australia is the 10th national health priority.

Pharmacogenomics is a field of precision medicine which seeks to apply knowledge of human genetic variation to inform and individualise medicine use. Improved health outcomes from pharmacogenomics are achieved through prevention of adverse drug reactions and gains in drug efficacy.

Several international consortia, including the Clinical Pharmacogenetics Implementation Consortium (CPIC®) and the Dutch Pharmacogenetic Working Group (DPWG), using international networks of experts assess the evidence for drug-gene pairs and publish the findings in peer-reviewed journals. The Pharmacogenomics Knowledge Base (PharmGKB.org) curates, and presents together for easy comparison, guidelines with clinically actionable drug-gene pairs from CPIC, the DPWG and others alongside drug labels from the US FDA and other regulatory drug agencies.

International guidelines and technological advances have facilitated a global expansion in the use of pharmacogenomics testing, albeit from a low base. Australia, like many countries, is unsure how best to integrate and utilise pharmacogenomics in the context of overall healthcare. Currently, Australian clinicians conduct few tests through either public subsidy or user pays private offerings.

Australia is well placed to increase the uptake of pharmacogenomic testing implementation and to improve medicine safety. Drawing on extensive experience from international implementations and growing evidence of value and utility will guide the process of incorporation of pharmacogenomics into clinical practice. Opportunities to further translation will present as the evidence develops and this should provide additional health and economic benefits.

The incubator project model, part of the Australian Genomics Grant Program (2021 – 2023), is about developing health genomic research priority areas considered to be of strategic importance to Australia. In pharmacogenomics, the model applies to promoting clinical translation and implementation of pharmacogenomic testing in the Australian healthcare system.

This report combines a landscape analysis of international pharmacogenomics activity and a national consultation with key stakeholders. The landscape analysis has explored international research, policy and exemplars of implementation into practice. The national consultation has explored Australia's current use of pharmacogenomics in practice, current and future barriers to expanding pharmacogenomic implementation and how they might be overcome, specific gaps that need addressing, and what future research could achieve if funded.

The report's key recommendations for Australia and pharmacogenomics are to:

- Expand pharmacogenomic testing where there is evidence to improve quality use of medicines.
- Establish a national steering network with individual and organisational representation for cross sector coordination and leadership.

- Conduct translational research in routine practice to produce evidence on clinical utility and cost effectiveness.
- Identify populations, therapeutic areas and contexts where pharmacogenomics could have a potential benefit.
- Develop local clinical guidelines leveraging international guidelines, international implementation exemplars and local evidence.
- Integrate pharmacogenomic clinical protocols into existing quality use of medicine practices and non-genetic clinical protocols (to ensure test results are not used in isolation); include indications for testing, result-informed therapeutic options and reporting guidance for laboratories.
- Develop models of pharmacogenomic testing services with practitioner roles. Include standards for patient consent and reporting.
- Secure subsidised access to selected pharmacogenomic tests (through MBS funding).
- Build practitioner knowledge through education and training (tertiary level and practitioner professional development).
- Develop supporting information technology (IT) infrastructure – options in electronic health records, interfaces between systems, clinical decision support tools (data storage, access, privacy, and reinterpretation capacity).
- Improve Australian pharmacogenomic reference data to include Indigenous populations and ensure representation of the ethnic diversity in Australia.
- Increase consumer awareness about the role of pharmacogenomic testing to improve health care and the safe use of medicines.

The report recommends three research priority areas for Australia:

1) Evaluation and implementation, 2) Models of service, and 3) Pharmacogenomics Education.

1. PROJECT AIM

The aim of this project was to conduct an international landscape analysis and national consultation to identify and develop recommendations for research priorities for implementation of pharmacogenomics testing in Australia. The report was submitted to the Medical Research Future Fund in September 2022.

The objectives were to:

- Provide justification for research into implementing pre-emptive and reactive pharmacogenomic testing in Australia to guide quality use of medicines.
- Understand the barriers and facilitators to the implementation of pharmacogenomic testing in the Australian healthcare system.
- Explore examples of international best practice.

2. RECOMMENDATIONS - RESEARCH PRIORITY AREAS FOR AUSTRALIAN PHARMACOGENOMICS IMPLEMENTATION

Research priority areas for implementation of pharmacogenomics in Australia have been identified and developed. They are presented below as separate research streams however, the streams of research are not meant to reflect funding streams; rather, **research should be conducted across streams, with collaboration between disciplines**. For optimal outcomes, funding models will need to have the flexibility to incorporate cross-stream research proposals.

Stream 1

Evaluation and implementation

Conduct research to better understand the role for pharmacogenomic testing in quality use of medicines, focusing on:

a. benefits, harms and cost-effectiveness, and the circumstances relating to setting of care, testing strategy and therapeutic area;
b. limitations and unintended consequences of testing, including ethical, privacy and social aspects;
c. experiences of patients and practitioners;
d. challenges to implementation (including barriers and enablers and feasibility), identification of implementation strategies to support the appropriate uptake of pharmacogenomics with plans to investigate fidelity in the future;
e. comparative evaluation of alternative courses of action to enable optimisation of costs and outcomes.

Stream 2

Models of service

Conduct research to develop and evaluate integrated models of service of pharmacogenomic testing with collaboration between healthcare professionals (including prescribers, pharmacists, laboratory scientists, clinical scientists/pharmacologists) and patients. The key lines of enquiry:

a. defining the processes and roles in various contexts for:
  i. pre-test patient counselling, referral, consent and ordering of tests.
  ii. interpretation and recommendations for treatment using pharmacogenomic results, non-genetic patient information and clinical guidelines.
  iii. presentation of reports containing results and recommendations
  iv. shared decision making and post-test patient counselling.
b. consideration of economic implications of each model.
c. digital health considerations that would see the integration of pharmacogenomics into the current electronic health infrastructure and clinical decision support tools.

Stream 3

Education

Develop nationally agreed competencies for education in pharmacogenomics:

a. university-level training
b. specialist training at the practitioner level
c. continuing professional development
d. on-demand training within clinical decision support

Guiding principles for studies of pharmacogenomics were identified from the literature and the national consultation participants. They state that studies should:

- Include Australia's population given Indigenous and ethnic profiles are underrepresented in the European dominated reference data that informs international guidelines.
- Be informed by international best practice.
- Consider: broad multi-gene panel tests and the informatics and practitioner stewardship resources required to realise ongoing utility; and point of care tests where time critical.
- Promote equity in testing (geographic and socioeconomic access).
- Consider pragmatic designs across various 'real world' contexts.
- Build workforce capacity for testing, utilising existing capabilities.
- Allow innovative models for evolving and future technologies such as polygenic scores for pharmacogenomics.

Population cohorts and indications where the potential benefit is high and the strong recommendation is implementation studies should consider these areas:

a. Candidates for drugs with known HLA hypersensitivity genes (test proactively, prior to prescribing and monitor after prescribing).
b. Individuals currently taking a drug with level 1A pharmacogenetic evidence[1] who have had an adverse drug event or lack of efficacy (test reactively to improve medication safety and efficacy, and to inform adverse event reporting databases).
c. Individuals being initiated on a drug with level 1A evidence where it is recommended in a clinical protocol and/or by a (credentialed) pharmacogenomic pharmacist (test proactively to improve medication safety and efficacy).
d. Individuals taking polypharmacy inclusive of a drug with level 1A evidence where it is the recommendation of a medication review pharmacist (test reactively to improve medication safety and efficacy).
e. Individuals being initiated on a drug where inadequate drug response could result in significant morbidity and mortality (e.g. anti-rejection medicines in transplantation, at time of diagnosis of severe or chronic conditions associated with multiple drug exposures, mental health, high cost medicines (financial impact)).

Justification for the recommendations (from the landscape analysis and national consultation)

Recommendation 1

- International experience and evidence provide rich guidance for local implementations. Limits to its generalisability arise from differences in healthcare systems and local healthcare environments including drug prices, test prices, formularies, funding and prescribing habits.
- Australia therefore requires local pharmacogenomic testing studies to demonstrate utility and cost-effectiveness, to understand the experience of patients and practitioners, and to explore unintended consequences.
- Despite up to ninety nine percent of individuals having an 'actionable' drug-gene variant most will not benefit from a test. We need to better identify populations with the **greatest**

[1] Level 1A is a clinical annotation score that means the drug-gene pair has met the highest criteria for level of evidence comprised of variant annotations, clinical guideline annotations and FDA-approved drug label annotations (see https://www.pharmgkb.org/page/clinAnnLevels).

clinical and economic benefit, meaning fewer people need to be tested to find one with the variant of concern. They can be identified by drug, therapeutic area, ethnicity or context.

- **Pragmatic study designs** are needed in real world contexts for assessing benefit and cost-effectiveness of pharmacogenomic testing. Real-world variables include non-genetic inter-individual response to medicine and the adherence of practitioners to recommendations and patients to medicines. The gold standard for collecting evidence in healthcare, the randomised controlled trial, may not be feasible or appropriate to generate the data needed to guide implementation of pharmacogenomics. Researchers need to consider appropriate endpoints for assessment: clinical and social benefits can occur months or years post-test (perhaps long after a trial has completed reporting).
- What to test for should be **guided by evidence, consensus and funding**. Multi-gene pharmacogenomic panel testing for preventing adverse drug reactions and improving medicine efficacy have lifelong utility. They are now of similar cost to single drug-gene tests: economic modelling suggests cost effectiveness is higher for panels over single gene tests. Some drug targets from early studies have been superseded by alternative drugs with less genetic variability (e.g. clopidogrel), or an objective phenotypic test embedded in practice protocols (e.g. warfarin).
- **Australian pharmacogenomic reference data** needs to represent Indigenous populations and non-European diversity. It would benefit from systematic follow up of adverse drug reactions inclusive of pharmacogenomic testing.

Recommendation 2

- **Models of service for pharmacogenomic testing** require collaboration between consumers and healthcare professionals (such as prescribers, pharmacologists, pharmacists and laboratory scientists). Evidence suggests collaboration is both feasible and valued. The literature has little consensus on service models and it remains unclear which practitioners are most suited for each role. Models should be informed by local context and be flexible to evolve as needed.
- **Key processes and roles in pharmacogenomics programs** performed by patient facing practitioners include: pre-test counselling and consent; test ordering; interpretation of the results with non-genetic information and relevant clinical guidelines; presentation of reports with recommendations; and post-test counselling and shared decision making with the patient.
- The resources currently used by practitioners contain **limited pharmacogenomic information and guidance**. Guidance with pharmacogenomic information proactively informs prescribing decisions, and reactively informs actions in the event of medicine harm. Knowledge and protocols should be at hand to ensure practitioners question whether a genetic factor is responsible and if a test is available.
- **Clinical decision support** is vital to utility and successful uptake of testing. It requires integration into practice software (that is, prescribing and dispensing software) for ready access to support treatment decisions at the point of care.

Recommendation 3

- A significant **barrier to wider implementation of pharmacogenomic testing in practice is the low level of practitioner knowledge**, competence and confidence to order a test or understand a report if it were presented. Building capacity lessens the impact on the current

healthcare workforce of predicted testing increases. With legal precedence having been established, practitioners without competence risk litigation.

- **Modules for pharmacogenomics** need to be included in practitioner education through curriculum development in university degrees and continuing professional development. Guidance can be taken from the US where it is a component of many pharmacy degrees and post-graduate certification is provided by several tertiary institutions.
- Poor practitioner **understanding of the foundational concepts of clinical pharmacology** should be acknowledged: pharmacodynamics and pharmacokinetics (absorption, distribution, metabolism and excretion of drugs (ADME)) and the drug metabolising enzymes which are involved in the majority of drug metabolisation. Many will be challenged to interpret pharmacogenomic results and competently guide prescribing decisions. Collaboration includes knowing personal limits and gaining ready access to expertise.

3. BACKGROUND

3.1 Adverse drug reactions

Medicines effectively treat and prevent acute and chronic conditions and help ageing populations to live well. The benefits we seek from medicines are, however, inseparable from their adverse effects. Pharmacogenomic testing can guide and improve our use of medicines to both prevent adverse effects and provide efficacy gains.

The impact of adverse drug reactions (ADR) on health care is significant. In Australia, medication-related problems cost the health system $1.4 billion and are the cause of 250,000 hospital admissions annually (1). It is assessed that half of medication-related harm is preventable. Medicine safety in Australia is the 10th national health priority (1).

3.2 Use of pharmacogenomic testing

The routine use of pharmacogenomic testing in practice is now possible, a situation achieved in recent years through public and private investment, technological advances and cost decreases. Testing has been introduced into various healthcare settings, from primary to tertiary care in North America and Europe, facilitated by state-sponsored implementation networks, and in a limited way in Asian countries with a greater prevalence of key genetic variants to one or two drugs. With most testing occurring in larger research-focused institutions or through user-pay commercial operations, it remains, however, somewhat niche and underutilised.

Public funding of pharmacogenomic testing is of a small scale in most jurisdictions globally, concentrating on the drugs with conclusive evidence of harm prevention, and the populations with a high prevalence of target variants. Australia first subsidised a test in 2007 for thiopurine methyl transferase (TPMT) and *HLA-B*57:01*, added a second in 2011 for abacavir and *HLA-B*57:01,* and since then there have been no further approvals.

Practitioners seeking to begin testing can be reassured by recent developments in the field, including: variant naming standards, provision of guidelines and national regulations. The star allele nomenclature was chosen to be the standard for naming variants in 2017 by an international workgroup (2). The clinical validity of drug-gene associations is reviewed and assessed by international consortia of experts, published in peer reviewed journals and collated into guidelines freely shared on the Pharmacogenomics Knowledge Base (PharmGKB.org). Regulation has been assumed by national drug agencies and many drug labels now include recommendations for using pharmacogenomic information for prescribing.

The main drug-gene variants of interest affect human leukocyte antigen (HLA) hypersensitivity, drug metabolism, or drug targets. HLA variants tend to be outliers with a greatly increased risk of severe and life-threatening reactions to drugs including abacavir, carbamazepine, allopurinol and phenytoin (there is a higher prevalence in Asian populations, although not all Asian countries are HLA testing (3)). Drug metabolism targets comprise the majority of identified drug-gene associations. Testing metabolism targets, however, is subject to evolving patterns of drug use. For example, drugs from early pharmacogenomic implementations have had their use somewhat superseded by alternative therapies with less genetic variability (e.g. clopidogrel) (4), or an objective phenotypic test

embedded in practice protocols (e.g. warfarin) (5). Drug targets are used predominantly in oncology and drug development fields and this topic is beyond the scope of the current project.

3.3 Challenges to wider implementation

An immediate challenge preventing scalable implementation, however, is the scarcity of evidence to demonstrate that testing is useful to patients and cost-effective to payers. The imperative for health systems is to identify where the most benefit might be. Recent enquiry has shifted its focus from single drug-gene pairs to multi-gene panels now that testing costs are similar, and, with lifetime utility, economic modelling suggests panels will prove more cost effective (6, 7). Large, multi-site, longitudinal implementation studies of panels in Europe and North America currently seek real-world evidence for their cost effectiveness and utility (8, 9).

Choosing a candidate population, condition or drug to trigger practitioners to test is not straightforward and requires a strong association between variant and response and an assessment of local health contexts and needs. Much of the current research activity is in psychiatric medicine where response differs with genetic variation in key enzymes of metabolism (*CYP450 2C19* and *2D6*) (10). The evidence to date leans towards a subgroup of people with moderate to severe depression and a previous psychiatric medicine exposure that caused an adverse effect or had poor efficacy (11). There is little evidence for pharmacogenomic testing at diagnosis of psychiatric illness (pre-emptively) to improve a person's initial medicine response (the likelihood of benefit and/or remission). A further candidate of interest is polypharmacy, a significant economic problem for health systems yet one where drug-drug-gene interactions can shift the complexity beyond current understandings of pharmacogenomics. No one candidate is perfect and other therapeutic areas, populations and individual medicines that offer potential will require careful consideration and evidence.

In Australia, Indigenous people have a higher prevalence of chronic health conditions, significantly poorer health and a lower life expectancy than the non-Indigenous population. Pharmacogenomics has the potential to improve Indigenous health by ensuring medicine choice and dose optimisation. Hampering the effort is the mostly unknown pharmacogenomic profile of Indigenous populations. The applicability of guidelines informed by European populations in non-European populations remains untested, yet evidence suggests the reduction in validity will have a negative impact on utility of this information in Indigenous populations (10).

Despite international experience and its promise, gaps in our understanding of pharmacogenomics remain. Yet, increasingly, primary healthcare practitioners are being exposed to pharmacogenomics in their practice and many have little knowledge or understanding of this area. It is a legal and moral imperative that primary health care providers have a working knowledge of this area of practice and are able to promote use of pharmacogenomics where appropriate.

3.4 Guidelines

Key points

- *Clinical guidelines are freely available online from the Clinical Pharmacogenetics Implementation Consortium (CPIC®), the Dutch Pharmacogenetic Working Group (DPWG) and others.*
- *The guidelines assign a level of evidence for each drug-gene association indicating the strength of the association and a recommendation to practitioners.*
- *The Pharmacogenomics Knowledge Base (PharmGKB.org) collects and curates into a single site pharmacogenomics guidelines and drug labels from key national drug agencies with pharmacogenomics information.*
- *Guidance on when to test or who to test can be found in approved product labels and other institutional practice protocols.*

The issue of trusted clinical guidance, arguably the most important facilitator to implementation of pharmacogenomics in clinical practice, has been addressed in recent years by several consortia and organisations. The evidence for clinically actionable drug-gene pairs is reviewed by international networks of experts and findings published in peer-reviewed journals and online (12). The key organisations producing guidelines are the Clinical Pharmacogenetics Implementation Consortium (CPIC®) and the Dutch Pharmacogenetic Working Group (DPWG). CPIC boasts expert membership from 29 countries making it truly international. Other notable guidelines are from the Canadian Pharmacogenomics Network for Drug Safety (CPNDS) and the French National Network (Réseau) of Pharmacogenetics (RNPGx)). A comprehensive review and comparison of the main guidelines was published in 2020 (13).

The Pharmacogenomics Knowledge Base (PharmGKB.org) curates, and presents together for easy comparison, guidelines from CPIC, the DPWG and others. PharmGKB also includes drug labels with pharmacogenomic information from regulators such as the US Food and Drug Administration (FDA), European Medicines Agency (EMA), Swiss Agency of Therapeutic Products (Swissmedic), Japanese Pharmaceuticals and Medical Devices Agency (PMDA) and Health Canada (Santé Canada) (HCSC). The Pharmacogenomics Global Research Network (PGRN), funded from the United States National Institute of Health (NIH), oversees CPIC, PharmGKB and PharmVar (a consortium for standardising the nomenclature used for pharmacogenomic genes).

In pharmacogenomic guidelines, a clinical annotation for a drug-gene association is assigned a level of evidence indicating the strength of the association using a 5-point scoring system: phenotype category, P values, effect sizes, cohort sizes and study types (14). In PharmGKB.org the levels are presented as 1A, 1B, 2A, 2B, 3 and 4. Level 1 is high level evidence for the association, level 2 moderate, level 3 low level and level 4 suggests the association between drug and gene is unsupported (14). PharmGKB Level 1A clinical annotations have '*variant specific prescribing guidance available in a current clinical guideline annotation or an FDA-approved drug label annotation*'. In July 2022, there were 289 clinical annotations with Level 1A evidence on PharmGKB.

Within a drug-gene pair annotation categorised as level 1 (A or B) there may be variants (poor, intermediate, rapid and ultrarapid) with different actionability (14). That is, the same annotation can have actionable ultrarapid metaboliser variants but not intermediate or poor metaboliser variants. For example, the common antidepressant amitriptyline has a Level 1A gene-drug annotation with various recommendations for the *CYP2D6* and *2C19* actionable variants:

> *The CPIC Dosing Guideline update for amitriptyline recommends an alternative drug for* CYP2D6 *ultrarapid or poor metabolizers and* CYP2C19 *ultrarapid, rapid or poor metabolizers. If amitriptyline is warranted, consider a 50% dose reduction in* CYP2D6 *or* CYP2C19 *poor metabolizers. For* CYP2D6 *intermediate metabolizers, a 25% dose reduction should be considered.* (PharmGKB.org - accessed online Feb2022)

Some annotations, such as the Level 3 annotation for amiodarone *CYP2D6* variants (below), have no recommendations. A pharmacogenomic report may choose to hide this information to minimise practitioner confusion.

> *There are currently no dosing recommendations for amiodarone based on* CYP2D6 *genotype.* (PharmGKB.org - accessed online Feb2022)

Less guidance exists for practitioners on which drugs to use pharmacogenomic testing before prescribing. CPIC for example, does not provide recommendations. Other organisations provide test gradings following an assessment of benefits versus risks (DPWG, CNPDS, RNPGx). They include 'essential' and 'strong level A' for high grades (13) and 'advisable' or 'possibly helpful' for lower grades. Approved product labels from the US Federal Drug Administration (FDA) and the European Medicines Association (EMA) include basic guidance on drugs and populations to test. They grade tests around notions of 'mandatory', 'recommended' and 'genetic test available for consideration'. Developers of practice software use this information for their clinical decision support.

Some recommendations in guidelines and product labels specify ethnic populations. For example, the FDA defines Han Chinese, Thai, Vietnamese, Indonesian, Malay, Filipino, or Indian descent populations as "genetically at-risk" due to a higher frequency of the *HLA-B * 1502* allele associated with adverse events to carbamazepine (10). It is standard practice to conduct an HLA test on all candidates for carbamazepine in Hong Kong, Thailand and Taiwan (10).

3.5 Regulation

Key points

- *The US FDA and other national drug agencies have assumed regulatory authority for pharmacogenomics, mandating pharmacogenomic data in product labels and drug registration applications, regulating laboratory developed tests and more.*
- *The FDA now has 209 and the EMA 94 drug labels with pharmacogenomics prescribing information.*
- *Labelling recommendations are not consistent (or harmonised) across agencies.*
- *Some regulators are moving to include pharmacogenomic data to improve genetic understanding of adverse events.*
- *Differing standards exist for regulating laboratory developed tests such as pharmacogenomics, and direct-to-consumer tests.*

Regulatory oversight of pharmacogenomics has been assumed by national drug agencies including the USFDA and others such as the EMA, Health Canada and the Japanese Pharmaceuticals and Medical Devices Agency. The FDA requires sponsors of drugs to provide genomic data relating to safety and effectiveness for inclusion in drug labels. Having pharmacogenomic information in drug labels improves overall practitioner awareness and understanding (15).

Recent global developments in the regulation of pharmacogenomics include harmonisation between national agencies of the information in drug labels and calls for industry to provide pharmacogenomic information for older drugs (16). It has been argued that regulators should encourage the practice of including pharmacogenomic testing in adverse event information (17).

Regulation from national drug agencies guides developers and providers of laboratory developed tests (LDTs) such as pharmacogenomics. The FDA defines LDTs as a class of *in vitro* diagnostic that is subject to medical device regulations in the Federal Food Drug and Cosmetic Act (18). The EMA has updated its regulatory framework to the 2017 IVDR that came fully into effect in EU Member States from 26 May 2022 (19). It covers the difficult to regulate software and algorithms used for predictions. Regulators are also considering direct-to-consumer pharmacogenomic tests around aspects such as clinical utility, safety and standardisation (20).

3.6 Pharmacogenomics in Australia

3.6.1 Public subsidy

The Medical Benefits Scheme (MBS) currently subsidises two single gene-drug pharmacogenetic tests - thiopurine methyl transferase (TPMT) and *HLA-B*57:01*[2]. They are indicated to screen for the genetic variants that increase the risk of severe adverse drug reactions, prior to prescribing.

[2] MBS data online accessed July 2022 at http://medicarestatistics.humanservices.gov.au/statistics/mbs_item.jsp

TPMT, listed in 2007, is an enzyme that breaks down thiopurine drugs (azathioprine, mercaptopurine and thioguanine), immunosuppressants for autoimmune conditions. Low levels of TPMT lead to bone marrow suppression. As of May 2022, 6,977 Medicare services have been processed for TPMT testing since its listing in 2007.

Testing for *HLA-B*57:01*, listed in 2011, is ordered prior to prescribing abacavir, an HIV treatment. The presence of the variant is linked to severe hypersensitivity reactions. As of May 2022, 64,668 Medicare services have been processed for *HLA-B*57:01* testing since its listing.

3.6.2 Australian regulation and product information

The TGA approved product information for the MBS listed items above do not mandate testing prior to prescribing[3]. Rather, they provide a recommendation as follows (our highlights):

> *Testing for* HLA-B*5701 *status* ***is recommended before initiating abacavir treatment*** *and also before re-starting abacavir treatment in patients of unknown* HLA-B*5701 *status who have previously tolerated abacavir.*
>
> *Patients* ***should be tested*** *for TPMT activity before starting azathioprine.*

For other medicines with pharmacogenomic information, the TGA product information contains a variety of broad statements and recommendations with little consistency and little specific guidance for practitioners and their patients on identifying who should be tested. Some examples (our highlights):

> *Clopidogrel - Consider alternative treatment or treatment strategies* ***in patients identified as*** **CYP2C19** ***poor metabolisers****.*
>
> *Allopurinol - Screening for* HLA-B*5801 *should be considered before starting treatment* ***in patient subgroups where the prevalence of this allele is known to be high****. Chronic kidney disease may increase the risk in these patients additionally.*
>
> *Carbamazepine - Testing for the presence of* HLA-A*3101 *allele should be considered* ***in patients with ancestry in genetically at-risk populations (for example, patients of the Japanese and Caucasian populations, patients who belong to the indigenous populations of the Americas, Hispanic populations, people of southern India, and people of Arabic descent)****, prior to initiating treatment with carbamazepine. The use of carbamazepine should be avoided in patients who are found to be positive for* HLA-A*3101*, unless the benefits clearly outweigh the risks.*
>
> *Testing for the prevalence of* HLA-B*1502 *allele should be considered* ***in patients with ancestry in genetically at-risk populations****, prior to initiating treatment with Carbamazepine Sandoz. If testing for the presence of the* HLA-B*1502 *allele should be performed, high resolution "*HLA-B*1502 *genotyping" is recommended. The test is positive if either one or two* HLA-B*1502 *alleles are detected and negative if no* HLA-B*1502 *alleles are detected.*

[3] TGA Product information accessed online July 2022 at https://www.tga.gov.au/product-information-0

*Codeine - … contraindicated for use **in patients who are** **CYP2D6 ultra-rapid metabolisers**.*

*Warfarin - **people with variations in two genes** may need lower warfarin doses than people without these genetic variations. The two genes are called* CYP2C9 *and* VKORC1*.*

Voriconazole - In vivo studies indicated that CYP2C19 *is significantly involved in the metabolism of voriconazole. This enzyme exhibits genetic polymorphism.*

The TGA further provides on its website 'Guiding Principles for Providers', published in 2014 by the National Pathology Accreditation Advisory Council[4]. Recommendation five is for direct-to-consumer (DTC) genetic pharmacogenetic testing:

Recommendation 5

The provider should not offer DTC pharmacogenetic testing without strongly advising the consumer not to initiate or alter the dosage of any existing medication, on the basis of the test results, without first consulting a relevant medical practitioner.

When providing consumers with the test results for pharmacogenetic tests, the test provider should strongly recommend that the consumer not alter the dosage of any existing medication on the basis of the test results and take the results of the pharmacogenetic test to a medical practitioner for personalised interpretation of the test result. The test provider should give the consumer appropriate information to take with them to their medical practitioner to aid the interpretation of the test results.

3.6.3 Key report and position statement

The Royal College of Pathologists Australasia produced a position statement in 2018 on pharmacogenomics with representation from Australia's medical colleges (21). It recommended expansion of pharmacogenomics testing in Australia and provided guidance for practitioners for implementation. The report suggested key facilitators to testing expansion, including:

- Adopt the CPIC guidance and develop local guidelines that are context specific.
- Determine the scope of use.
- Ensure medical supervision for testing and no direct-to-consumer testing.
- Provide clinician education at tertiary and practitioner development levels.
- Increase funding for translational research on implementation in various healthcare settings.
- Apply for MBS funding for tests with high utility and validity evidence.
    - funding should be extended to cover tests for 'DPYD *(to identify patients at risk of toxicity from 5-fluorouracil and capecitabine) and* HLA-B*1502 *(to identify patients at risk of carbamazepine-induced hypersensitivity reaction)*.'
- The college should engage with stakeholders such as '*patients, funders, medical schools and specialty colleges and the pharmaceutical industry and pharmacists.'*

3.6.4 Pharmacogenomic reference data in Australia

In pharmacogenomics, key guidelines ensure the validity of associations between genetic variants and drug responses. As with other fields of genetics they overwhelmingly rely on studies using

[4] *Accessed online June2022 at https://www1.health.gov.au/internet/main/publishing.nsf/Content/health-npaac-genetictestguide)*

populations with European ancestry in Europe and the US. Non-European populations are understudied and have less certain links between genetic predispositions and drug response (22).

Australia does not have a significant national database of pharmacogenomic reference data. This means that Australia's unique pharmacogenomic landscape has not been adequately studied. In comparison, the UK government has completed its 100,000 Genomes Project and has a target to whole genome sequence 500,000 of its population by 2023-24 (23).

Underrepresented populations in genetic studies are frequently overrepresented with respect to existing health disparities. Without their inclusion in pharmacogenomic studies, health disparities will worsen (24). Because of past traumas and cultural sensitivities, study participation of Indigenous populations requires consultation, trust, long term relationships and transparency (22). Overcoming barriers increases the opportunities for Indigenous populations to equally benefit from pharmacogenomics. Ethical concerns in studies can be addressed by promoting Indigenous control of sensitive data collection and use. A priority is to train Indigenous researchers and develop Indigenous research guidelines (22).

3.6.5 Current Australian studies in pharmacogenomics

Many pharmacogenomics studies are currently underway in Australia. The following list (table 1) includes the major studies listed on https://www.australianclinicaltrials.gov.au/clinical-trial-registries (accessed online 29Jul2022).

Table 1: Current Australian pharmacogenomics research trials

STUDY TITLE (Trial ID)	ALLOCATION	END POINT	TARGET SAMPLE SIZE	RECRUITMENT STATE
Pharmacogenomics guided antiplatelet selection strategy prior to intracranial or carotid stenting (383017)	Non-randomised trial		80	NSW
GLAD Study: Genetics Linked to Anti-Depressants in Adults with Treatment Resistant Depression (382784)	Randomised controlled trial	Efficacy	60	WA
Pharmacogenetics for Severe Mood Disorders: A Randomised Controlled Trial (381268)	Randomised controlled trial	Efficacy	800	VIC
Pre-treatment dihydropyrimidine dehydrogenase (DPYD) genotyping in patients receiving fluoropyrimidine (5-Fluorouracil or Capecitabine) chemotherapy: A clinical implementation study of the effect of individualised dosing on treatment related toxicity (381432)	Non-randomised trial	Safety	280	QLD

AustraLIan trial of GeNotype-guided pharmacothErapy for Depression (ALIGNED Study) (381841)	Randomised controlled trial	Efficacy	776	NSW QLD SA WA VIC
Towards implementation of pharmacogenomics-guided therapy in patients with mental illness - Stage Preliminary (P) and Stage 1 (ENACT) (381577)	NA	Model of care, Experiences	260	NSW
Pharmacogenomics guided dosing for fluoropyrimidine and irinotecan chemotherapies for patients with cancer (PACIFIC-PGx) (381022)	Non-randomised trial	Safety	630	NSW, VIC
PRESIDE (380870)	Randomised controlled trial	Efficacy	672	ACT NSW NT QLD SA TAS WA VIC
Does genetically guided antidepressant prescribing improve outcomes in depression? (365100)	Randomised controlled trial	Clinical outcomes	150	VIC

3.6.6 Special interest group

The Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT) is the Australian and New Zealand professional and independent society providing expertise around the use and toxicity of medicines. Its pharmacogenomics special interest group has an active membership of pharmacists, pharmacologists and scientists working in the field of pharmacogenomics. The ASCEPT annual scientific meeting is a focus for advancing pharmacogenomics research from laboratory to implementation.

3.6.7 Information management for genomics

The Australian Government has recently turned towards developing a National Approach to Genomic Information Management, which includes approaches to infrastructure for storage, analysis and sharing of genomic information (25). Preliminary recommendations developed by Australian Genomics have proposed a national, standards-based approach, using a federated cloud or hybrid model comprised of three critical pillars: interoperability for interactions between systems; scalability for growth and big datasets; and extensibility for expansion.

Recommendations are for a coordinating entity and funding of an implementation pilot. The next stage, due mid-2022, is a more comprehensive report and roadmap.

4. REVIEW OF INTERNATIONAL BEST PRACTICE, APPROACHES AND HEALTH SYSTEM INTEGRATION

4.1 Methods

A review and analysis of the pharmacogenomics literature was conducted. Electronic databases were searched in October 2021 for reviews of pharmacogenomics and for specific topics, such as 'practitioner experience'. Reference lists were searched to identify further relevant studies. Key pharmacogenomic networks and consortia were searched for relevant literature. Relevant literature was included from weekly alerts and subscriptions in pharmacogenomic special interest groups in Australia and internationally during the project.

4.2 Summary

Key points

- *Testing is expanding globally yet there are no primary care national implementation examples (26).*
- *Large multi-site programs in the US and Europe are building capacity (currently in 27 US institutions) (27).*
- *Most testing in routine practice is conducted by lone practitioners and mostly for single drug-gene pairs e.g. abacavir, clopidogrel, warfarin, codeine.*
- *Models of service are influenced by institutional resources and differ with respect to practitioner roles and responsibilities. They should include collaboration between different healthcare practitioners and flexibility to respond to changing needs and evidence (28, 29).*
- *Knowledge among practitioners and the public is generally poor.*

The field of pharmacogenomics is expanding. The US and the European Union are funding large implementation programs. Multi-site trials, such as GeNomics In practice (8) and Pre-emptive Pharmacogenomic Testing for Preventing Adverse Drug Reactions (PREPARE) (9), are building an evidence base that will strengthen the case for translation into mainstream practice. In the US, there are 27 pharmacogenomic programs operating in hospitals or medical facilities attached to universities or research centres (26, 27, 30).

Many of the barriers to implementation have now been addressed. Practitioners can draw on evidence-based pharmacogenomic guidelines, pharmacogenomic data on product labels from national drug agencies, and cheaper, faster tests. Yet, testing numbers remain low, no jurisdiction has achieved national implementation (31) and many services amount to a lone practitioner outsourcing a few tests to a commercial organisation (9). The literature often describes pharmacogenomics in terms of *unfulfilled potential* (27, 31).

Meanwhile, several large programs continue to evolve and lead, moving beyond single drug-gene pairs to multi-gene panel tests with potential for lifelong utility (8, 32). Economic modelling suggests

panels will be cost-effective (6), however, more clarity is needed on their value proposition in real-world practice which key studies in the US and Europe will provide.

Health systems in most countries are grappling with questions around how best to implement pharmacogenomic testing in an equitable and cost-effective way. Existing public programs are limited, reflecting the resources and needs of each health system and population. Generally, pharmacogenomic testing is limited to one or two high-value drug-gene pairs. Recent literature provides insight into pharmacogenomics implementation internationally:

Canada	Pharmacogenomics in Canada is described as siloed and lacking large scale national studies to facilitate and evaluate implementation (33).
UK	Planning a '*gradual and iterative*' implementation of testing through the National Health Service (NHS) building on investment in genome sequencing for rare diseases and cancers including a National Genomic Test Registry (listing available tests, protocols for ordering and technology required) and a National Genomic Testing Service. A recent joint report from the British Pharmacological Society and the Royal College of Physicians (23) details implementation recommendations (see 6. Current Directions and Future Trends).
Netherlands	Led the field with the Dutch Pharmaceutical Working Group guidance. It has integrated guidelines and test ordering into practice software for both prescribers and pharmacists. Test reports are included in electronic patient health records (34).
Asian countries	With relatively high frequencies of HLA variant polymorphisms many provide screening prior to prescribing some drugs (Japan, Singapore, Thailand, Hong Kong, China). Thailand, with high rates of HIV, tests prior to antiretrovirals (35).
African countries	Building reference data with non-European genetic diversity and creating hubs of implementation excellence (36). Priority in Sub-Saharan Africa is improving safety and efficacy of treatments for HIV, TB and malaria (37).
South American	Reporting suggest large genetic heterogeneity from admixture that differs between countries is a challenge for implementation and research (37).

4.3 Practitioner roles/ Service design

Key points

- *The main gatekeepers for ordering tests are practitioners (prescribers or pharmacists).*
- *Interpretation of results into recommendations includes consideration of non-genetic patient factors, current prescribing guidelines and concomitant medicines.*
- *Interpretation is conducted by prescribers, pharmacologists, or pharmacists: in-house for larger institutions or outsourced to external laboratory or providers.*
- *Pharmacist roles cross all aspects of services, clinical pharmacologist roles include oversight, resource development and advisory.*

There is a mature body of implementation literature from early adopter programs, some of which have been operating for over two decades. Implementation recommendations emphasise multidisciplinary and flexible service models with the capacity to evolve as required by changing technologies and local contexts (29, 38, 39). Most service models give importance to the following interconnected elements:

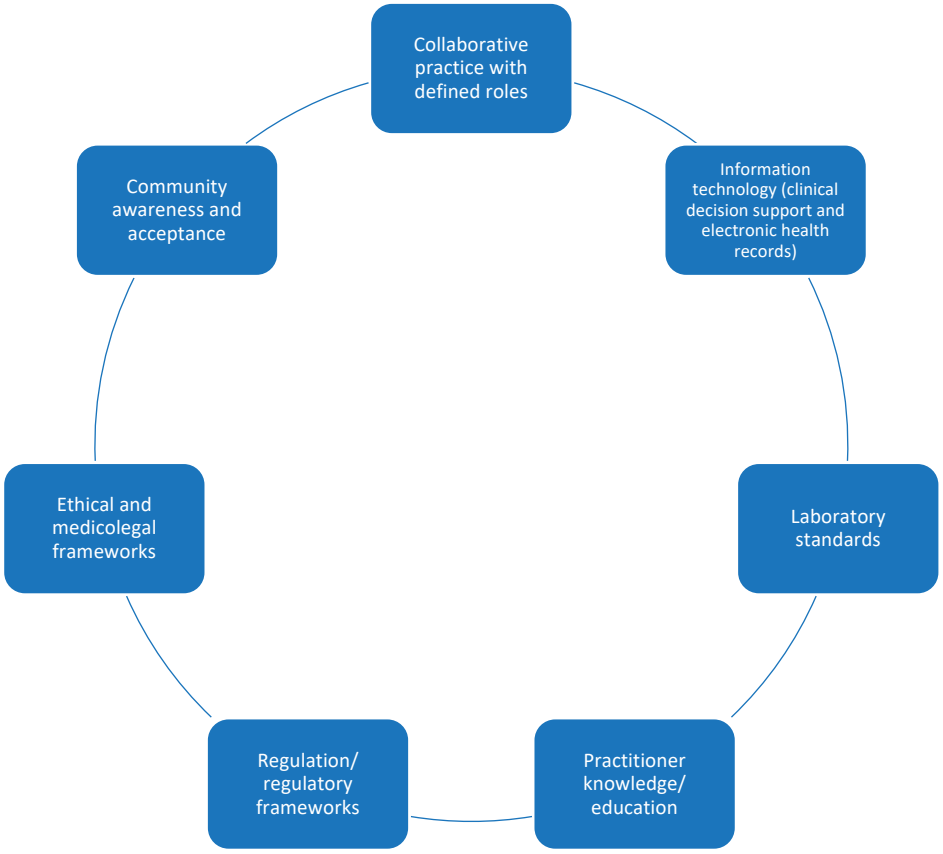


Figure 1: Interconnected elements required for a pharmacogenomics service

Testing services vary according to the type of test (pre-emptive or reactive), the medicine of interest, and the available turnaround times for receiving test results back from laboratories (10). Highly resourced programs can draw on centralised expertise with physicians, pharmacologists and

pharmacists to assist in interpretation as well as provide oversight and resource development (10). In routine primary care settings, interpretation work is generally outsourced to commercial providers (40). Practitioners with clinical support tools integrated into practice software are assisted in their decision making yet this is not available or affordable to all health services (10).

A key requirement for the success of a testing service is providing patients and practitioners with results that are meaningful. Pharmacogenomic test results are most useful when presented with recommendations as a summary and report to patient facing practitioners (41). They can then be integrated into the broader clinical picture of each patient including, where necessary, age, gender, concomitant medicines, renal function, inflammation, smoking, diet, and weight (10). Pharmacogenomic testing is one part of overall medicine management that includes prescribing guidelines, appropriate monitoring and regular review (17, 39). Pharmacogenomic reports should be equally accessed by all relevant practitioners to ensure collaboration and to facilitate successful and sustainable service provision (27, 42).

In primary care, several defined roles or tasks are required to provide pharmacogenomic testing services (29). They are pre-test counselling, obtaining consent, ordering tests, receiving results, interpretation with consideration of non-genetic patient factors, coordinating with other practitioners, writing report summaries with recommendations, uploading to electronic medical records and post-test counselling of patients.

Service differences generally relate to the level of resources available as well as the individual champions who lead and drive them, a role frequently taken on by pharmacists (29). Pharmacists are prominent in the implementation literature performing roles including interpretation and review of results, recommendations to prescribers, transfer of results into EHR, patient counselling and assisting prescribers not accustomed to pharmacogenomics (20, 39-41, 43). It has been demonstrated that prescribers trust and value pharmacists to present clinical recommendations to them, and that they lack the time to interpret reports themselves (44-46).

Further, pharmacists chair multi-disciplinary oversight committees, develop CDS and provide educational resources (47). Several key programs in the US are led by pharmacists (48). Many primary care and hospital settings have pharmacogenomic stewardship roles provided by pharmacists that have demonstrated feasibility and sustainability (44, 46, 49, 50). Stewardship provides a point of contact for practitioners and ensures actionable results are actioned.

4.4 Indications for pharmacogenomic testing

Key points

- *Up to 99% of people have at least one actionable drug-gene variant, although most are never relevant to the carrier.*
- *Identifying people who will most benefit from testing is an imperative for implementation where resources are limited.*
- *Indicators for testing include individual drugs, drug types, therapeutic areas, genetic ancestry, conditions etc.*
- *Currently, most testing is reactive prior to initiation of higher risk/evidence drugs such as abacavir, azathioprine, clopidogrel, warfarin, codeine and others (51).*

The fact that actionable drug-gene variants are carried by up to 99% of people suggests there is huge potential for pharmacogenomic testing in improving medicine safety and efficacy (8). An actionable variant, however, does not confer clinical utility as most variants are not relevant to the carrier now or in the future. The challenge for pharmacogenomics service providers is how to identify and prioritise those who will receive benefit from testing. Indicators for testing may be individual drugs, therapeutic areas, genetic ancestry, condition or disease, or polypharmacy.

Practitioners' willingness to order pharmacogenomic tests is improved by third-party funding yet with little new evidence of utility and cost-effectiveness, submissions to funding bodies are scarce (26). Obvious candidate drugs for further funding are the HLA associated drugs. However, despite the potentially large safety gains from preventing HLA associated severe drug reactions, the low prevalence of the variants of concern in many populations still means that cost-effectiveness of testing is borderline (52).

A 2016 implementation review suggested that a pharmacogenomics service begin with the following six drug-gene pairs - '*HLA-B and abacavir and carbamazepine; CYP2C19 and clopidogrel; TPMT and azathioprine, mercaptopurine, and thioguanine; CYP3A5 and tacrolimus; CYP2D6 and opioids; and CYP2C9/VKORC1 and warfarin' (53)*. Since 2016, prescribing trends have significantly changed for many of these drugs including newer alternatives on the market that do not require pharmacogenomic testing. Further, few sponsors are willing to gain evidence and apply for funding for testing of older drugs. A 2018 paper proposed categorising drug-gene pairs with a clinical implementation score calculated by the associated clinical effect, level of evidence and number needed to genotype (NNG) (34). The categories for pharmacogenomic testing would be '*potentially beneficial', 'beneficial' and 'essential'*, similar to some guidelines.

A change in the way benefit is assessed is required with the emergence of multi-gene panels and their potential lifelong utility. Each panel can be set to test a range of variants and value is therefore unique (10). The U-PGx study includes a panel with the most common actionable variants from DPWG guidance and patients are identified by the first prescription of one of 42 drugs of interest (54). The PREDICT study uses a panel of 16 drugs (55). Commercial offerings typically use pre-

determined panels of common variants with well-defined associations and recommendations (27, 56).

The utility of testing can be increased through exploiting differences in the genetic landscape between individuals of European, Sub-Saharan African, Oceanian, Asian, South-East Asian, Middle Eastern and other regions (3). Recommendations for testing genetic ancestries with high prevalence drug-gene variants are included in some approved drug labels and clinical resources (see 3.4 Guidelines). In Australia's multi-cultural population, the effect of admixture and inaccurate self-assessment of genetic ancestry are limiting factors. Panels built for European populations may miss variants seen in non-European ancestries (10).

Identifying individuals for testing can be done by an indicator condition or pharmacological category (for example, cardiovascular, central nervous system, cancer) (17). The Canadian IMPACT trial focuses on mental health and uses a panel of genes relevant to psychiatric medicines (IMPACT Canada). In mental health, the strongest evidence for pharmacogenomic testing is for adults of European ancestry with major depressive disorder and a previous non-response or adverse reaction to a psychiatric medicine (10, 57).

Polypharmacy is associated with a high likelihood of medicines with actionable variants (44), more serious medicine problems (58), and poor concordance with directions (29). In a number of small studies, pharmacogenomic testing of individuals taking polypharmacy reduced adverse events, provided savings in healthcare utilisation and improves adherence (44, 59-61) yet its use and benefits remain understudied (11). Knowledge in this area is limited and phenoconversion from drug-drug and drug-gene-drug interactions adds extra complexity (45).

Pre-emptively testing all consenting patients with multi-gene panels remains the privilege of well-funded exemplar US programs (18, 49). In theory, testing all citizens at birth using a multi-gene panel maximises utility but is too costly and resource intensive for the foreseeable future (26). NHS England's Genomic Medicine Service is discussing the use of whole genome sequencing in routine care and have stated aims of sequencing 500,000 whole genomes by 2023/24 (23). Patient cohorts have been used as indicators for pharmacogenomic testing. An example is renal transplantation, to guide immunosuppressants and antimicrobials (23, 38).

The turnaround time for receiving test results may be an important factor in utility depending on the indication. The turnaround time required in antibiotic prescribing for an acute infection would clearly need to be shorter than for prophylaxis in scheduled surgery. A longer turnaround time may be possible for chronic condition medicines such as statins for cardiovascular disease. Less urgency to deliver results should not, however, unduly inconvenience patients.

4.5 Clinical decision support, electronic health records and data storage

Key points

- *Clinical decision support (CDS) is a key facilitator to practitioners' use of pharmacogenomics yet is costly to develop and maintain with updates (12).*
- *In-house CDS tools were developed with early adopter programs and continue to evolve.*
- *There are a growing number of commercial CDS tools.*
- *Literature on CDS tool evaluation is minimal (62).*

New health interventions require robust tools to streamline workflows, lessen the burden on practitioners and preserve time with patients. For pharmacogenomics, clinical decision support (CDS) tools deliver alert warnings at the point of care - pre-test for high-risk drugs and post-test for at-risk genotypes (41, 55). They are considered the most influential facilitator to practitioner uptake of testing (55). Key functions are about automating much of the process and, as such, CDS tools depend on being integrated with electronic medical/health records which store pharmacogenomic patient profiles and other health records (27, 29).

Absent or fragmented CDS and electronic health records reduce the utility of testing (63). For electronic health records, the big issues are about how data is stored, its security and access. Patient access to pharmacogenomics records can benefit other practitioners by alerting them to its existence, useful such as when travelling across different jurisdictions.

Development and implementation of CDS is costly. Early adopter US programs were aided by significant institutional infrastructure, expertise and funding (8, 41, 44). Typically, they developed CDS in parallel with program implementation, beginning with a single drug-gene pair to ensure feasibility and safety, and adding drug-gene pair 'rules' when additional evidence allows. The DPWG have integrated pharmacogenomic guidance, test ordering and patient reports into prescribing and dispensing software (64). The European U-PGx PREPARE trial includes a CDS tool based on DPWG guidance in multiple languages that integrates with the different electronic health records in each participating country. Despite their importance, there appears to be little scholarship evaluating CDS tools (62).

Several challenges have been identified around implementation of CDS tools. Poor patient health records and medicine lists impact the integrity of CDS alerts, and the recommendations provided to practitioners - potentially missing some or creating others that are not valid (18). Poor communication between stakeholders and other human factors require training and mentoring (64, 65). Appropriate staffing levels are a significant and challenging barrier to overcome.

CDS development is now more costly than laboratory expenses, even before ongoing management and updating with emerging evidence (12). The experience of some institutions suggests that the responsibility for ongoing expense is an area of potential conflict (12). Countries without electronic health record systems can consider a QR code system such as developed in the UPGx where with a smart phone a person's unique QR code opens a website with recommendations for their

pharmacogenomic profile (54). A similar idea, the genetic ID card, is used in Thailand for individuals with HLA polymorphisms (66).

The website https://cdskb.org/ is an online repository and resource for CDS tools.

4.6 Practitioner knowledge and education

Key points

- *Practitioners have low levels of knowledge and confidence in their ability to use pharmacogenomics.*
- *Small increases in testing levels will impact current health workforces.*
- *Direct-to-consumer tests drive practitioners to upskill.*
- *Free online pharmacogenomics resources and education are available for practitioners.*

Practitioners' engagement with pharmacogenomics is hindered by their poor knowledge levels and associated lack of confidence (27). It is predicted that health workforces will be pressured when testing numbers increase, and lack of readiness will exacerbate the pressure (24, 67).

Building practitioner knowledge is a challenge that has not been solved in the context of a national implementation. It will likely require education and training across multiple professional groups and specialties (30). In the last ten years, more medical, pharmacy and nursing schools have begun providing pharmacogenomics education, although at 1-2 hours per degree program there is more work to be done (68). Increases in direct to consumer (DTC) testing in the US are driving practitioners to seek education (46).

Pharmacogenomics education is most effective when it includes more than one mode of delivery and is integrated into the resources and educational platforms that practitioners already use (29). It requires local and national leadership. The UPGx implementation program used a 4-day training program encompassing knowledge, skills and attitudes for practitioners (69).

Several online resources freely provide practitioner education for pharmacogenomics:

www.pharmgkb.org	Provides links to several educational materials.
www.mydruggenome.org	Vanderbilt University Medical Centre education portal.
www.ce.mayo.edu	Mayo Clinic online resources.
www.upgx.eu	UPGx e-learning education resources platform.
www.stjude.org/pg4kds	St Jude Children's Research Hospital educational resources.

4.7 Evaluation of pharmacogenomics testing

Key points

- *Analytical and clinical validity have been addressed through laboratory accreditation and evidence-based guidelines e.g. CPIC.*
- *To date, much of the evidence for value of pharmacogenomic tests remains unclear (70).*
- *Test value should be assessed in real-world application studies (71).*
- *Current trials are seeking evidence for improving drug safety and efficacy using pre-emptive panels (42).*

The translation of pharmacogenomic testing into clinical practice is underpinned by assessments of analytical validity, clinical validity, clinical effectiveness, clinical utility and cost effectiveness. Analytical and clinical validity assess the ability of a test to detect the variant of interest and predict a drug response respectively. Clinical effectiveness, clinical utility and cost effectiveness are assessments of the outcome, usefulness and economic value of a test. There remains a paucity of utility and cost-effectiveness evidence for pharmacogenomics testing, and it is considered unlikely that many of the established drugs with less defined genetic markers will ever reach an evidence threshold, nor funding and time for trials (9).

Efforts to elicit positive clinical and cost-effectiveness outcomes from tests are challenged in several ways. Most obviously is that variants of interest have a low prevalence in general populations and, ipso facto, the cost of conducting numerous tests to find one person with a variant of interest is high. More common variants tend to dominate effectiveness studies yet rare variants contribute to poor medicine safety (72). The concept of number needed to genotype (NNG) is a useful comparator of variant prevalence (73).

Randomised controlled trials (RCTs) with optimised conditions, prioritised in evidence-based medicine, are not always feasible for assessing the effectiveness of testing in real world practice (71). Measuring pharmacogenomic testing outcomes in these settings requires prospective 'real-world' trials. Trials, whether observational cohort studies or other randomised or non-randomised trials should be pragmatic in design (71). Consistency in primary endpoints, frequently lacking, will facilitate future combining of trial evidence. Warfarin studies for example, have used both bleeding events and the international normalised ratio (INR) as study endpoints (5).

Utility points to the usefulness or value of pharmacogenomic testing in clinical practice, that is, the influence on clinical decision making and the outcomes that are important to individuals and family (12, 74-76)). Utility may require that effective actions are available, such as dose adjustments or alternative treatments. It is inclusive of psychosocial, ethical, legal and social aspects. Unintended consequences of testing are included in utility assessments such as equity effects from the withdrawal of effective treatment options for some individuals, and changes in practitioner behaviours (74, 77). An example of an unintended consequence occurred in Hong Kong following

mandated testing for carbamazepine: prescribers changed prescribing habits and increased adverse events resulted from increased phenytoin prescribing (12).

A strong assessment of benefit is more likely when variants of interest are associated with severe adverse reactions *and* have a high frequency. An example is a variation in the *HLA-B*5701* allele linked to a higher risk of severe skin reactions with the HIV medicine abacavir. This association is generally described as an outlier and subsidised screening prior to prescribing abacavir has been in place in many countries, including Australia, for more than 10 years (26). Even so, some countries with lower population frequencies of the *HLA-B*5701* variant have not assessed routine testing as cost-effective (3). Along with prevalence in a population of variants, the assessment of cost-effectiveness strongly relies on each health system's hospital costs from severe reactions (78).

Pharmacogenomics does not explain all variation in medicine response and this is a challenge for collecting evidence of benefit. Many non-genetic factors such as age, sex, body mass index, diet, and concomitant drugs determine the response to a medicine in people carrying the same genetic variant. For warfarin, only 40% of inter-individual variability can be attributed to the two genes commonly tested, *CYP2C9* and *VKORC1* (5, 79). Additionally, outcomes cannot be achieved unless practitioners adhere to test recommendations and patients to medicines - an indirect effect (80). Few studies report on practitioner adherence to recommendations (81).

Complex economic modelling is being used to assess value for pre-emptive panels (6). Models require assumptions of future savings for healthcare utilisation and medicines to treat future health conditions and costs of ongoing data storage. Software is required to enable access at the point of care when needed and reinterpreting of results with updated evidence. In real-world studies, a further challenge is assessing the indirect costs of undertreatment that may occur over many months or years.

4.8 Cost and clinical effectiveness evidence

A selection of recent reviews of cost and clinical evidence categorised by indication is presented below in table 2:

Table 2. Recent evidence reviews for cost and clinical effectiveness

Category	Cost evidence	Clinical evidence
General		
	• Verbelen et al. 2017 review of cost-effectiveness studies was inconclusive in part due to large cost differences between countries for tests and adverse event care (78). • Plumpton et al. 2021 developed an evaluation framework for a multi-gene panel to prevent adverse reactions and found cost-effectiveness in many, but not all indicator drugs (6).	• David et al. 2021 review found pharmacogenomic testing led to medication changes and lessened frequency of all cause hospitalisation compared to treatment as usual (81).

HLA

- Zhou et al. 2021 reviewed HLA risk alleles across ethnicities in 74 countries and found allele frequency a key factor in predicted cost-effectiveness thresholds for abacavir, carbamazepine and allopurinol. Included was the number of patients who would be unnecessarily denied the drug of interest after a positive screening. The authors recommended countries with heterogeneous populations consider subpopulation-specific differences (52).
- Kloypan et al. 2021 suggested HLA screening requires population with greater than 2.5% prevalence of at-risk alleles to be cost-effective (82).
- Manson et al. 2020 reviewed the diagnostic criteria for HLA testing and found that while specificity is high the sensitivity varies between drugs (abacavir, allopurinol and carbamazepine having the highest) (73).
- Kloypan et al. 2021 review suggested there is strong evidence to consider clinical use of HLA alleles for reducing the risk of drug induced adverse reactions (82).

Mental health

- Li and Loshak's 2020 review found conflicting evidence regarding cost-effectiveness of pharmacogenomic testing for prescribing in depression (included HTA, reviews, and economic evaluations). Applying findings across health systems was not possible due to variability, low quality primary data and differing assumptions and methodologies (83).
- Bousman et al. 2021 review concluded testing in mental health can save cost through reduced healthcare utilisations, pharmacy costs (from switching medicines) and costs of adverse reactions (10).
- Carrascal-Laoo 2021 found, in schizophrenia with previous poor response to medicines, savings in hospitalisations and medicine use greatly outweighed testing costs (84).
- Bousman et al. 2019 review and meta-analysis of five RCTs found depressive symptom remission is more likely with pharmacogenomic guided treatment than without, risk of bias present from industry involvement in primary studies (11).
- Rosenblat et al. 2018 review concluded pharmacogenomic guided treatment in major depression may improve response and remission but limitations of data heterogeneity, testing company funding and enhanced placebo effects mean further well designed studies needed (85).
- Li and Loshak's 2020 review was inconclusive regarding effectiveness of pharmacogenomic testing in depression (83).
- Ielmini et al. 2022 review and meta-analysis found testing reduced adverse effects in major depressive disorder and bipolar disorder yet improved efficacy only in major depressive disorder (86).

- Marshe et al. 2020 found inconclusive evidence of benefit for testing for antidepressants in older adults and issues with primary studies (87).

Cardiovascular

- A review by Zhu et al. 2020 found testing for cardiovascular drugs was cost effective in 2 of 3 studies (mostly clopidogrel and warfarin) (88).
- Shah 2020 found warfarin testing cost ineffective, suggesting pharmacogenomic spending should be redirected elsewhere (5).

- Wu 2015 review found warfarin pharmacogenomic testing did not reduce adverse events such as stroke or bleeding. Suggested there is potential to identify individuals with variants who should be initiated on alternative anticoagulants (89).
- Shah et al. 2020 found warfarin studies had poor design and findings of low clinical relevance that are unable to be replicated in real-world settings. Non-genetic interindividual variance around 60% (5).
- Galli et al. 2022 reviewed the evidence of guided P2Y12 inhibitors (clopidogrel, prasugrel, and ticagrelor) to explore balance between ischaemic and bleeding risk. Found guided therapy reduced incidence of major adverse cardiovascular events and bleeding but not for all indications (4).
- Chora and Burboun 2021 review found little evidence for pharmacogenomic testing for statin prescribing (90).

DPYD

- White et al. 2022 review of DPYD testing for dose adjustment of fluoropyrimidines found evidence of cost-effectiveness. Health system expense differences account for huge variance (91).

- White et al. 2022 review of DPYD testing for dose adjustment of fluoropyrimidines found morbidity reduced without negative efficacy effects. The authors recommended expansion of implementation (91).

Polypharmacy and medicine review

- O'Shea et al. 2022 review found limited evidence for efficacy of pharmacogenomic testing in

		polypharmacy and issues with study design and size (92).
Other non-review evidence	• Maciel et al. 2018 economic modelling for pharmacogenomic guided treatment in depression found cost-effective in real-world clinical settings (93). • The PREDICT study found that panel testing lowered the number of subsequent single tests needed by 60% (27).	• Bank et al. 2019 estimated that 1 in 19 prescriptions commonly prescribed in primary care would have dose adjusted or switch to another drug if pre-emptive panel test with eight pharmacogenes used (94).

4.9 Practitioner perceptions and beliefs

Key points

- *Practitioners self-assess low knowledge and confidence with pharmacogenomics.*
- *Leadership and institutional support facilitates use of testing.*

Enquiries into the views of practitioners have mostly focused on identifying barriers to the uptake of pharmacogenomics in practice. Concepts that have been applied include readiness, uncertainty, willingness and acceptance.

Self-assessment of readiness includes views of the need for testing, which are typically positive, and of competence, knowledge and skills, which are typically low (27). Practitioner uncertainty with their own knowledge stems from no exposure to training (undergraduate and post-graduate) and a perceived lack of guidance on when and what to test, although most had never sought to access available resources (95). Confounding generational cliches, 20–39-year-old practitioners were less likely to adopt testing than the 40–59-year-old age bracket.

Practitioners revealed their willingness to order tests would increase with (53, 95):

- More regulatory approval from national regulatory bodies,
- More evidence of clinical advantage of testing or not testing.
- Recommendations from colleagues or experts in the field - a ‘physician champion’.
- Adoption of clinical practice guidelines by professional organisations and others.
- Trialling of exemplar drug-gene pairs with strong evidence.
- Targets and other evaluation tools to demonstrate the clinical value back to practitioners.

Decisions to test are guided by context specific formal and tacit rules, norms and practices that need to be considered (75). Individual practitioners, patients, families and broader society may have moral concerns to acknowledge. For implementation Smart (75) suggests we need to understand:

- That knowledge of a new area of practice is gained from both training and experience.
- The organisational context where practitioners operate.
- The broader social norms and values that shape practitioners' actions.

Aligning closely with willingness, practitioner acceptance of pharmacogenomic testing increases with use of testing and availability of guidelines and clinical decision support tools (27, 96), as well as ease of institutional implementation (48). Acceptance of an implementation takes account of individual beliefs around clinical efficacy and is influenced by external validation from respected bodies or approved guidelines (48). Acceptance depends on ease of processes, accessibility of the presentation of test results and familiarity with alternative options. Time can be a factor particularly with return of results.

Prescriber acceptance further depends on unexpected factors which perhaps highlights the need for careful planning. Prescribers, for example, were more likely to implement recommendations in an elective surgery setting for opioids (97) than for clopidogrel (98). The study authors suggest that one of the factors may be an aligning of purpose between opioid stewardship and pharmacogenomics (97). The availability of alternatives can be a significant factor to prescriber acceptance (99).

While eliciting the views of patients to identify concerns or alleviate unfounded perceptions is seen as important, practitioners revealed time as being a barrier to actually doing it.

4.10 Ethical, Legal and Social Implications

Key points

- *Pharmacogenomic tests differ from most genetic tests as they link to clear interventions.*
- *Testing requires gaining of informed consent.*
- *Pharmacogenomic testing risks increasing existing inequalities.*
- *Using racial qualifiers to screen for testing may have unforeseen impacts.*

Ethical, legal and social implications (ELSI) of pharmacogenomics first received scholarly attention at the time of the Human Genome Project completion in 2003. Enquiry was along similar lines to genomic germ line testing and included test error, confusion with results, stigmatisation, familial implications and discrimination (100). The potential to uncover unwanted data with harm and no utility was considered (100).

Genetic exceptionalism, the belief that genetic data is fundamentally different from other forms of data due to being uniquely identifying and highly predictive, does not appear to be an issue for pharmacogenomics. The gap between genome and phenome is significant for the majority of associations meaning pharmacogenomic testing is not highly predictive. More reliable and more predictive non-genetic tests such as kidney function further dispel the exceptionalism belief.

What further distinguishes pharmacogenomic test results from most genetic tests is their clear link to interventions, that is, they inform drug treatment decisions (100). The ethical focus of pharmacogenetic tests should therefore be on a broader consideration of information revealed and any associated patient implications (101). It is a requirement that practitioners gain informed patient consent that includes prior consideration of the purpose and clinical utility of the proposed test.

It is important to consider the risk of pharmacogenomic testing programs furthering health inequalities in populations with already poorer health from other determinants, yet this has received little academic enquiry (24). Magavern et al. suggest broad engagement and involvement of communities in implementation planning and ongoing evaluation of the uptake of test services and inequalities in distribution (24).

While using racial qualifiers for testing (and research) has utility for stratifying people to identify those with a higher likelihood of variants to target healthcare and maximise cost efficacy, it is important to consider other impacts of labelling. Assumptions about genetic variability between race constructs are a risk to equitable healthcare and should be avoided. There is considerable genetic diversity within populations and self-determined ancestry does not always match genetically determined ancestry. Magavern et al. and Luczak et al. recommend using the term 'genetically determined ancestry' or 'genetic ancestry', however, it is an imperative that any labelling as such is only used where there is a clear purpose (24, 102).

Equity and justice considerations include: the risk of ethnicity being used as a reason to withhold access to medicines in place of a genetic test (for reasons such as willingness to pay, availability of service or practitioner choice) if variants are more highly represented in that population (24, 103); being left with no effective therapy (orphan genotypes) (103); and the risk of individuals with multiple backgrounds being marginalised (24).

The 2003 Nuffield report suggested that direct to consumer sales be avoided where test results will present complex information and where predictions have variable certainty (101). Others have expressed similar concerns about reliability and ability to interpret some tests and the risk of patients adjusting or stopping medicines without advice (103). Bioethicists consider the potential psychological harm that may eventuate from patient access to complex data.

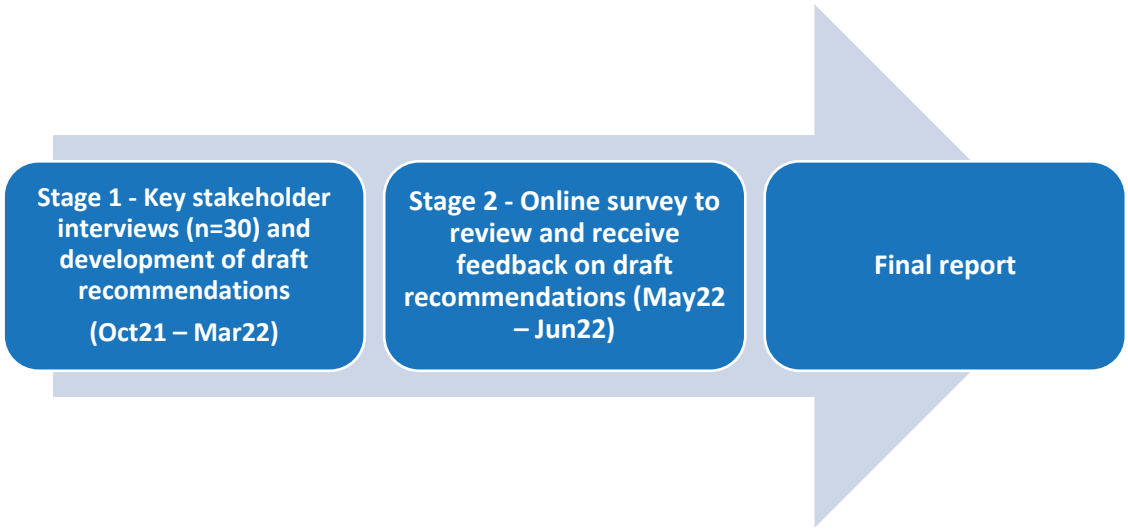
Genomic organisations considering how to improve equitable engagement and participation are:

The Global Alliance for Genomics and Health	https://www.ga4gh.org/
Global Indigenous Data Alliance	https://www.gida-global.org/
ELSI 2.0 for Genomics and Society	https://doi.org/10.1126/science.1218015

5. NATIONAL CONSULTATION - WHAT ARE THE RESEARCH PRIORITIES FOR AUSTRALIA AROUND IMPLEMENTATION OF PHARMACOGENOMICS TESTING?

5.1 Methods

The national consultation was conducted in two stages. Firstly, in-depth individual interviews to explore the views of key stakeholders and develop draft recommendations and, secondly, a follow-up online survey to reflect the draft recommendations from the interviews to a wider stakeholder cohort for feedback.



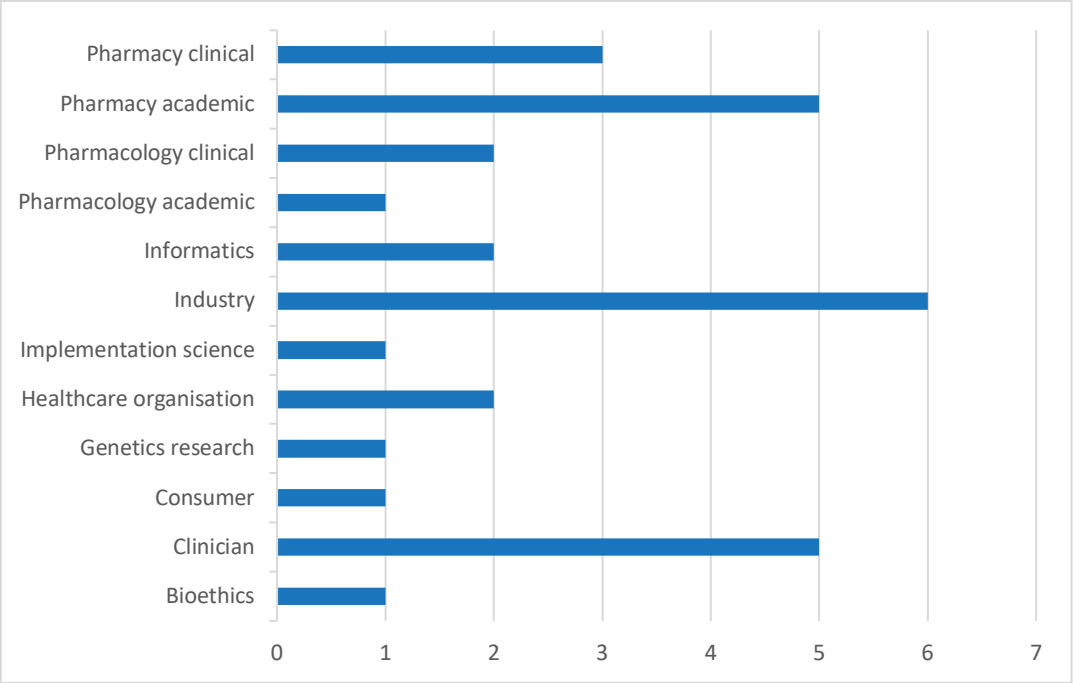
Stage 1 - Key stakeholders in the field of pharmacogenomics were identified using contacts of the research team, pharmacogenomics networks in Australia, literature searches for Australian authors in the field, and snowballing. Individual interviews were conducted (n=30) between Oct 2021 and March 2022. Interviews followed a semi-structured format and lasted between 50 and 70 minutes.

The interview participants' relevant disciplinary knowledge and skills included medicine, clinical pharmacology, pharmacy, ethics, public health, psychiatry, industry, bioinformatics, Indigenous health and consumer. They were geographically located across Australia and internationally (see table 3).

Participants were informed of the project aim: to identify the research priority areas around implementation of pharmacogenomics into the Australian healthcare system. Interviews explored Australia's current state of practice implementation, current and future barriers to implementation and how they might be overcome, specific gaps that need addressing, and what a future research collaboration could achieve if funded.

Interviews were transcribed and analysed thematically around the interview topics. Interview themes and understandings from the international literature review were used to develop draft recommendations and research priorities for Australia.

Table 3. Stage 1 interviews by sector.



Stage 2 - An online survey created in REDCap[5] was used to reflect draft recommendations and research priorities developed from the interview themes back to the interviewees and an expanded stakeholder group (Appendix 4). The survey was emailed to individuals and relevant organisations for distribution to their members. Over 150 people viewed the survey and 64 responses were received.

The responses were analysed and used to update the draft recommendations for the final report.

5.2 Summary (review)

The key message from the national consultation is Australia needs to expand pharmacogenomic testing to improve medicine use. Interview participants noted the existence of international guidance providing clinical validation of drug-gene pair variants, and international exemplars providing a roadmap for implementation in Australia. They believed the focus for Australia is now on demonstrating the circumstances where testing has utility and identifying the requirements for achieving scale. Key areas that require consideration for wider translation into practice include cross sector collaboration, development of various models and settings of care, appropriate regulation, building of expertise and training opportunities, and designing integrated information technology with clinical decision support.

It was suggested that Australia begin its expansion of testing where harm is easily identified, and its prevention is possible. To this end, several medicines associated with identifiable genetic variants and severe adverse reactions have annotations in CPIC guidance, international implementation

[5] https://www.project-redcap.org/

exemplars and a mature body of evidence around clinical utility in various contexts. Required, are local clinical protocols with clear indications for testing and public subsidy.

Participants wanted Australian research investment to be directed into implementation studies to identify further areas where testing has utility. Studies should preference high prevalence variants and/or those with a strong association between the genetic marker and drug response, meaning fewer people need to be tested to find one with the variant of concern. The general agreement was studies should use multi-gene panels, align with the clinical needs of the population tested and ensure equitable access through diverse practice settings across geographic areas and socio-economic gradients.

It was noted that testing pharmacogenes for future use (pre-emptive) requires considerable data storage and protocols around access to the data, as well as addressing of ethical, legal and social concerns. Advances in testing technology enabling cheap whole genome sequencing will further expose health system weaknesses around data storage, retrieval and interpretation capacity that need to be overcome. If clinical utility is best gained by having test results available at the point of care when they are needed, then it is likely that at some point in the future all new-born babies will be offered genetic screening.

Adding to the complexity of gaining evidence of clinical utility is the imperative for the evidence to represent the diverse ethnicities found in Australia. Participants highlighted that, as in other areas of genetics, equitable application of pharmacogenomics is limited by Eurocentric data. Further, the genetic architecture of Australia's Indigenous populations is poorly understood and, along with high levels of medicine use to treat chronic conditions in these populations, should be an important consideration in decisions around prioritising research funding.

Participants want future Australian research to trial, develop and evaluate several models of care with respect to practitioners, processes and reporting. Collaboration across disciplines should be a starting point for all service designs. Education needs to be expanded so more practitioners are competent to apply pharmacogenomics appropriately in their practice.

The importance of practitioners having realistic expectations for pharmacogenomic test results was emphasized by participants. They believed pharmacogenomics should be conceptualised as an additional marker with both strengths and limitations for real-world practice, a view currently far from universal. Many drug-gene associations do not provide clinicians with a definitive answer and practitioners should consider pharmacogenomics testing as *"just another tool in the toolkit"* or "*piece of the jigsaw puzzle"*, providing insight into inter-individual variability for the same medicine in efficacy and adverse drug reactions. Clinical decision support should be made available to guide the appropriate use of pharmacogenomic testing.

5.3 Guiding principles for expansion of pharmacogenomics

Several themes emerged during the consultation process about how participants believed pharmacogenomics implementation *should* progress in Australia to advance its appropriate use. They are provided here as *guiding principles*:

- Use of pharmacogenomic testing is underpinned by informed consent, shared decision making and person-centred care.
- Testing is purposed for achieving meaningful outcomes for people, avoiding low-value care and unintended consequences.
- Evaluations of utility look beyond economic measures to include social and ethical dimensions, particularly where a pharmacogenetic test can prevent harm.
- Practitioners are competent, collaborative across disciplines and supported by clinical protocols that integrate genetic and non-genetic information.
- Testing includes pharmacogenetic reference data that represents Australia's unique genetic ancestry.
- Equitable access across geographic and socio-economic gradients is a goal of implementation.
- Testing services should not exacerbate existing inequities.

5.4 What is the current state of pharmacogenomics in Australia?

The participants described the current state of pharmacogenomics in Australia as:

- A small but increasing number of tests are conducted (both publicly and privately funded) from an increasing number of service providers, including direct-to-consumer.
- Turnaround times for test results can be long, up to three weeks.
- Public funding for tests through the Medical Benefits Scheme (MBS) is only for two drug-gene pairs.
- TGA categorises all tests in the same class - moderate to high risk (Class 3 in-vitro medical devices).
- There is little evidence of cost-effectiveness and clinical utility in local contexts.
- Australian genetic reference data is limited, Indigenous pharmacogenes are mostly unknown.
- Poor knowledge and awareness among practitioners means the workforce is unprepared, similarly there is little public knowledge.
- Evidence-based models of service have not been developed.
- Standards-based data options are absent for storing and accessing reports, sharing across jurisdictions, or integrating with clinical decision support.
- Research activity is siloed in small trials and single-site hospital settings, resulting in little post-trial practice change.
- Clinical champions are few as is political will to break status quo.

5.5 Themes

Themes were identified from the participant interviews around requirements for implementation of pharmacogenomic testing in Australia (see Figure 2).

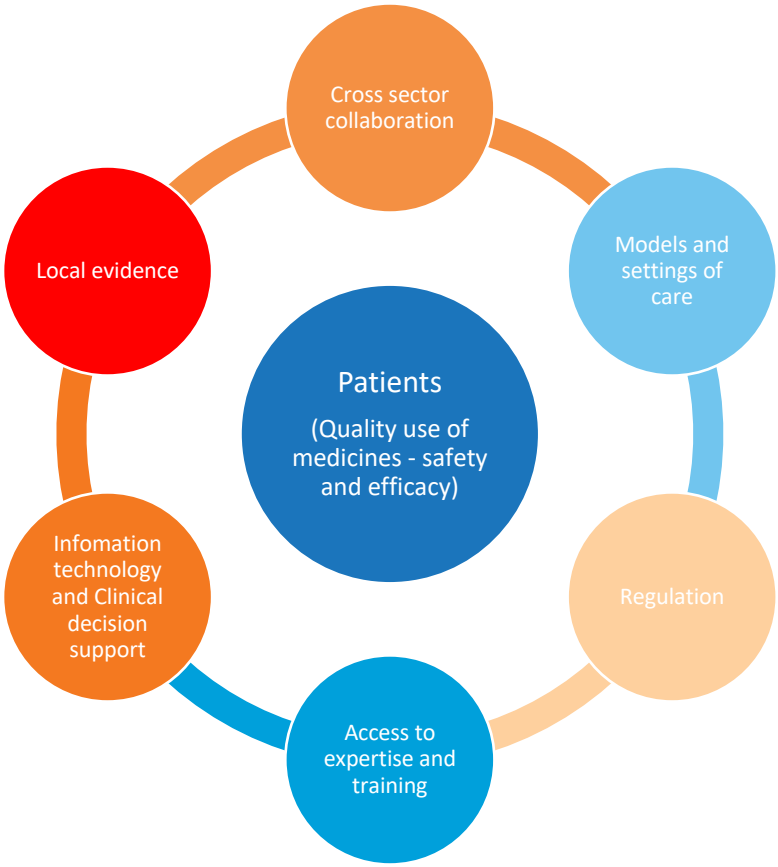


Figure 2: What needs to be considered for implementation in Australia?

5.5.1 Cross sector collaboration

Expanding the use of pharmacogenomic testing in Australia will require a coordinated national effort such as the national steering or working groups, consortia, or networks seen internationally. Participants suggested an Australian network draw from the key health organisations and professional bodies (the specialties, pathology, pharmacy, general practice, nursing and others). Representatives of industry and the developers of Australian practice guidelines such as the Australian Medicines Handbook, Therapeutic Guidelines, Mims and the National Prescribing Service are important stakeholders.

Champions are required to demonstrate implementation success, and mentor peers and future practitioners. They may be high-profile individuals who have adopted pharmacogenomic testing in their practices and institutions. Moreover, champions might be a specialty or therapeutic area willing to test models of service, processes, resources and capacity, and thus inform translation and implementation in other areas. An example is psychiatry where, currently, several Australian pharmacogenomic trials are in progress.

5.5.2 Models and settings of care

Participants deemed a one-size-fits all model for pharmacogenomic testing services as not feasible. Rather, several models should be developed and trialled, taking into account different healthcare settings and local needs. Roles and processes would be determined by the purpose for testing and the context. For example, a model for guiding antibiotic and/or opioid prescribing in a hospital setting, identifying those at risk of adverse effects and undertreatment, might pre-emptively test at admission. One for improving current and future medicine use in polypharmacy or renal disease in a general practice or aged care setting might test a broad panel. A pharmacist home medicine review (HMR) model might include a protocol where indicator medicines with level 1A CPIC evidence are an alert for testing.

Collaboration is the starting point for service design. Participants emphasised sharing of knowledge, responsibilities and workloads in service models. Multi-disciplinary team approaches from primary to tertiary care are required to facilitate appropriate testing and use of pharmacogenomic results. Equally important, is not creating new structures, rather, building on those currently accepted and available.

Data interpretation requires practitioners with a sound understanding of clinical pharmacology principals, genomics and disease management. Interpretation includes competent integration of pharmacogenomic data with non-genetic data, coordination with other practitioners, and appropriate communication of clinical advice and recommendations. Clinical scientists and pharmacists doing therapeutic dose monitoring should be part of the team. Interpretation and integration of results into the clinical picture is made more complex in the instance of polypharmacy, multi-gene panels, co-morbid conditions, psychosocial factors, patient preference and phenoconversion.

Participants spoke of the impact of the turnaround time for testing on several elements of testing services. Turnaround time affects the use and usefulness of testing and, in turn, influences its uptake. It increases when referral to a second practitioner is required to order a test, swabs can only be taken at external collection points, and results are not readily available to all practitioners. Equal capacity to order tests and access results and other necessary health data should be afforded to prescribers and pharmacists.

It was argued by participants that a pharmacogenomic service model would benefit from inclusion of a stewardship role. Stewardship aligns with the conceptualisation of pharmacogenomics as having an important but integrated place in medicine management with clinical and medicine histories, renal and liver function tests, drug interactions and therapeutic dose monitoring. The steward would be the point of contact in the team, assisting practitioners and consumers, and following up inquiries. Stewards would guide and inform on practice guidelines and clinical protocols.

5.5.3 Regulation

Participants argued that regulation has a major responsibility in setting the parameters for use of pharmacogenomic testing. Further, regulation serves to inform and reassure practitioners, providing

standards and certainty to laboratories and industry. As such, regulatory bodies such as the TGA need to further integrate pharmacogenomics into policy documents and approved product information. Exemplar regulators for Australia are the leading international agencies such as the FDA and EMA. Genetic testing laboratories in Australia are accredited by NATA, a similar role is performed by CLIA and CAP in the US.

Participants suggested further regulations to define aspects of pharmacogenomics including:

- Standards for tests:
    - What is included in a general panel test, that is, what gene-drug variants should be tested as a minimum?
    - What is included in a panel test designed for a specific therapeutic area, such as psychiatry or cardiovascular?
    - What is a low value test?
    - What are the standards for direct-to-consumer testing and reporting?
- Which practitioners can interpret/report and what further training/accreditation is required?
- What is the standard for a pharmacogenomics report?
    - Which results should be prioritised and how? For example, a traffic light system.
    - Which results should be hidden? For example, variants of low significance/benefit that may confuse practitioners and consumers.
- What are the standards for storage, access and use of data?

5.5.4 Access to expertise and training

Participants indicated that a key barrier facing uptake of testing in practice is poor knowledge among Australian practitioners about pharmacogenomics, a predicament common to health workforces globally. Moreover, it is a significant system constraint that few practitioners have adequate competence to order and interpret pharmacogenomics reports. Both the number of practitioners with pharmacogenomics knowledge and their depth of knowledge need addressing.

It was emphasised that educational resources require developing for practitioners in tertiary degrees and continuing professional development programs. Guidance can be taken from the US experience where pharmacogenomics is a component of many pharmacy degrees and post-graduate certification is provided by several tertiary institutions. An intermediate step may be the online resources provided freely by several international networks, although they would not always align with Australian contexts with respect to available medicines and clinical protocols. Education for practitioners at the point of decision making can be integrated into clinical decision support.

Participants from Australia's laboratories suggested they have laboratory capacity to respond to expansion of pharmacogenomics testing but inadequate numbers of skilled practitioners capable of interpreting test results.

A concern raised is poor prescriber understanding of foundational concepts of pharmacology key to pharmacogenomics. Specifically, this includes the principles of absorption, distribution, metabolism and elimination (ADME), pharmacodynamics (PD) and pharmacokinetics (PK) and the cytochrome P450 enzymes involved in the majority of drug metabolism. As most pharmacogenetic variants

tested for are associated with changes in PD and PK, the shortcomings highlighted are a hurdle that will prevent practitioners attaining a meaningful understanding of pharmacogenomics and its place in guiding medicine use. While crowded medical curriculums may prevent its inclusion, pharmacy degree programs at university level already provide in-depth teaching of these concepts, strengthening the case for pharmacists in multi-disciplinary teams.

5.5.5 Information technology and clinical decision support

It was identified by participants that the key resources used by Australian practitioners contain only scant information concerning pharmacogenomic aspects of medicines. There is little in TGA approved product information, The Australian Medicines Handbook, Therapeutic Guidelines, MIMs, NPS MedicineWise and discipline specific guidance developed by professional bodies and colleges. The legitimacy of pharmacogenomics and the reassurance practitioners require to feel confident ordering tests is limited by not being present in the resources currently used by practitioners.

Visibility and accessibility of pharmacogenomic information are key for practitioners' use. Pharmacogenomic information needs to be readily available at the point of care, integrated into tools and resources to guide decisions. Treating practitioners should have access to knowledge and guidance around the possibility of a genetic factor being responsible and whether a genetic test is available if a patient is experiencing harm from a medicine.

One of the contemporary challenges for Australian healthcare services highlighted by participants is patient data storage. The national electronic health record (MyHealth Record) is the preferred option but does not, as yet, accommodate pharmacogenomics reports. Other potential issues affecting pharmacogenomics include a lack of standards for data and multiple patient records that are not connected in formats such as portable document formats (pdf) that cannot be interfaced with contemporary bioinformatics systems. Pharmacogenomics reports need to be at once secure and accessible to treating practitioners at the point-of care. An idea floated by participants in the instance of MyHealth Record remaining unsuitable is a central exchange for storage and secure access. It was highlighted that storage costs are significant and, in the case of pharmacogenomic data with life-long utility, ongoing.

Challenges more specific to pharmacogenomics include the inherent complexity of genetic reports and of conceptualising risk in a meaningful way. Care should be taken to ensure patients are not side-lined by this complexity and, as such, electronic records should be in a patient-centred format and stored to ensure patient accessibility. Electronic records should function as a mechanism for enhancing patient engagement and scrutiny and facilitating transferability between health services in different jurisdictions.

Clinical decision support was described as vital to the utility and usage of pharmacogenomics by practitioners. It should be integrated into practice software (prescribing and dispensing) such that prescribers have ready access to reports and guidance to support treatment decisions. The cost of initial development and the ongoing maintenance costs required to ensure currency are significant and require early negotiation.

Pharmacogenomic clinical decision support needs to be interfaced with the practice software yet, in Australia, prescribing and dispensing software differs in patient care settings in hospital, general practice and specialties, and across local and state jurisdictions. While participants agreed that integrated clinical decision support tools are vital to the use of pharmacogenomic testing, not all agreed that it was a research priority appropriate for public funding.

5.5.6 Local evidence - research priorities and study designs

When the research priorities for implementation of pharmacogenomics into Australian healthcare were considered, participants consistently spoke of the imperative to gain evidence in real-world practice of benefit and cost-effectiveness and the circumstances in which these align. That is, identifying who should be tested and when they should be tested to achieve value from testing. When considering what to test, there was agreement that Australian research should follow contemporary study exemplars and include as many pharmacogenes as practical in a single panel, to gain future utility. It was emphasised that the views of practitioners and patients need to be part of any evaluation.

Research should be directed to developing and evaluating different service models in the Australian healthcare system. The priorities for inquiry are around: who can order tests, how they order them, who interprets the results, how the results are presented, and how they are actioned and followed up in a timely manner to be useful to the patient.

Finally, citing generally poor awareness and knowledge of pharmacogenomics, participants spoke of the need to develop various educational offerings including tertiary training for health practitioners, continuing education for current practitioners and patient resources.

Participants emphasised the need to carefully consider study design. Most agreed that randomised controlled trials were not feasible or practical for evaluating interventions in real-world practice, yet others believed them necessary to progress the field. Different aims and contexts will require different study designs.

Other study elements that were emphasised include:

- Inclusion of various settings - primary care, hospital and others.
- Demonstration of capacity for collaboration between different healthcare practitioners in the ordering, interpretation, and actioning a test.
- Inclusion of implementation scientists, health economists and other relevant non-clinical researchers.

A significant challenge to cost-effective implementations is being able to identify the populations most likely to have an actionable variant of interest. Some key characteristics suggested are that the population is identifiable, has a high prevalence of actionable variants and regular practitioner contact. A target population proposed as an exemplar and disciplinary champion is psychiatry, or mental health. The reasons provided include:

- Psychiatric medicine has a growing evidence base of medicines with actionable genetic variants, that is, variants that if present lead to meaningful drug or dosage decisions.

- Psychiatry has less objective phenotypic markers than other therapeutic areas such as cardiovascular disease.
- Mental health has a significant disease burden and increasing prevalence.
- Patients interact with multiple health professionals in both hospital and primary healthcare systems - exposing greater numbers of practitioners to pharmacogenomics more quickly.
- Depression has many drug treatment options and testing has the potential to aid the decisions.

Trials should occur over enough time to accrue benefits from test interventions. The greatest cost savings are likely to be gained through reducing hospital presentations and admissions. A challenge for implementation is that test beneficiaries (those reducing healthcare costs) are unlikely to be test funders, particularly in the Australian healthcare system where primary care is funded nationally and hospitals are funded by each state or territory.

6. CURRENT DIRECTIONS AND FUTURE TRENDS

6.1 Similar healthcare systems

A 2022 report jointly released by the British Pharmacological Society and the Royal College of Physicians aims to guide the expansion of pharmacogenomic testing across the four UK nations (23). It gained endorsement from 12 UK professional colleges and societies and a forward from the chair of NHS England.

The report's main recommendations are that pharmacogenomics be implemented into primary, secondary and specialty settings for the 'wide range of drugs that have actionable pharmacogenomic recommendations available'. Other recommendations include: implementation should be agile so as to respond to further updates and newly discovered drug-gene pairs; practitioners should have access to education and support services; and ongoing research should be funded. Notable in the report, is the absence of a recommendation for compelling economic evidence *prior to* implementation.

According to the authors, challenges for expansion of testing are in the following areas:

- Designing the clinical service
- Standardising consent
- Providing laboratory capacity
- Storage and access to results across different paper-based and electronic health systems
- Practitioner knowledge
- Gaining public trust
- Securing funding

The national Genomics Education Programme, one of numerous organisational bodies that have been created, has been tasked with educating practitioners and workforce planning. Their 2021 review of educational offerings found an absence of pharmacogenomics in curricula, standards, continuing professional education and competency frameworks.

The report recommended multi-gene panel testing as the standard for most tests for ongoing utility and cost effectiveness gains. Other offerings include rapid point-of-care testing and single drug-gene pair assays that can be returned within 30 minutes. Results from panel tests should only display drug-gene pairs where the indication has been approved. As such, additional drug-gene pairs will be assessed according to:

- Frequency and severity of clinical outcomes that are associated
- The quality and consistency of the evidence base
- The effect size of the genetic variant
- Indications for testing and feasibility
- The number of patients that are anticipated

Pharmacogenomics in the UK will benefit from a national goal to have the whole genome sequenced for 500,000 individuals. The associated infrastructure includes a national network of centralised laboratories and the National Genomic Test Registry. The UK has commenced screening for DPYD

variants prior to prescribing fluorouracil to test process and capacity, utilising existing sequenced data where possible.

Australian researchers and policy makers will find guidance and areas for collaboration from the partnership between the two British organisations.

6.2 Pharmacogenomics and the MRFF Missions

The Genomic Health Futures Mission is one of eight MRFF Missions. Future pharmacogenomic research may benefit from closer alignment with four of the missions as shown below in table 4.

Table 4: Where can pharmacogenomics research align with the MRFF missions?

MRFF Mission	Potential for pharmacogenomics research
The Cardiovascular Health Mission brings together researchers, health professionals, industry and patients to make transformative improvements in heart and vascular health and stroke for all Australians.	Cardiovascular drugs with 'actionable' variants. Guide prescribing to reduce adverse events and improve clinical endpoints.
The Dementia, Ageing and Aged Care Mission supports older Australians to maintain their health and quality of life as they age, live independently for longer, and access quality care when they need it.	Improve quality use of medicines and avoid preventable adverse events.
The Indigenous Health Research Fund supports Indigenous-led research to tackle health issues facing Aboriginal and Torres Strait Islander people	Guide treatment for chronic diseases affecting a large proportion of populations e.g. cardiovascular, metabolic and psychiatric medicines. Indigenous pharmacogenomic database.
The Million Minds Mental Health Research Mission supports Australians with mental health issues by enabling access to new approaches to prevention, diagnosis, treatment and recovery.	Current pharmacogenomic research funding in mental health is for guiding new and existing therapies. Develop new service models.

6.3 Other

6.3.1 Polygenic scores and pharmacogenomics

It is likely that the field of pharmacogenomics will increasingly utilise polygenic scores to improve drug response predictions. Pharmacogenomic polygenic scores are gaining evidence either by themselves or with disease risk polygenic scores as a single assay, such as in psychiatry. A recent review suggested the evidence is still preliminary and more transparency is required for studies around risk model development and data and adoption of reporting standards (104). Common issues

include Eurocentric data and the need for adequate base and target sample sizes for genome wide association studies.

6.3.2 Legal challenges

Recent cases in the US have set precedents for ongoing legal challenges. The Hawaiian state successfully sued the manufacturers of the anti-coagulant clopidogrel, claiming it had not been informed its Pacific Island and Asian populations are more likely to have genetic variants with reduced efficacy (105). In Oregon, a claim for negligence was made against a hospital from the spouse of a patient who died from capecitabine, claiming the hospital did not conduct a pharmacogenetic test prior to prescribing as is recommended in annotations from CPIC and DPWG on PharmGKB.org (106).

7. FINAL COMMENTS

The momentum seen globally, particularly from key organisations and government healthcare, suggests use of testing will continue to increase. An opportunity for Australia to guide medicine use, reduce adverse drug reactions and improve efficacy is available through broadening the use of pharmacogenomic testing into primary healthcare settings.

Demonstrating clinical utility and cost-effectiveness in Australian contexts is a requirement for mainstream acceptance and use of pharmacogenomics. Moreover, development and evaluation of models of practice and education will be integral to successful health system implementation. These are the key research priority recommendations from this consultation and report.

Pharmacogenomics testing is being used and will continue to be used in parts of healthcare. It is unlikely that research in isolation will ensure its use is equitable. Leadership, supporting infrastructure and regulation are required to ensure benefits for this new technology are shared in Australia.

ACKNOWLEDGEMENT

The authors of the report thank the many researchers, practitioners, ethicists and others with an interest in pharmacogenomics for participating in the interviews and online survey and for giving their considered, informed thought to the future of pharmacogenomic research and implementation in Australia.

8. REFERENCES

1. Pharmaceutical Society of Australia (PSA). Medicine Safety: Take Care. Canberra; 2019.
2. Kalman LV, Agúndez JA, Appell ML, Black JL, Bell GC, Boukouvala S, et al. Pharmacogenetic allele nomenclature: International workgroup recommendations for test result reporting. Clinical Pharmacology & Therapeutics. 2016;99(2):172-85.
3. Zhou Y, Lauschke VM. Population pharmacogenomics: an update on ethnogeographic differences and opportunities for precision public health. Hum Genet. 2021(141):1113-36.
4. Galli M, Benenati S, Franchi F, Rollini F, Capodanno D, Biondi-Zoccai G, et al. Comparative effects of guided vs. potent P2Y12 inhibitor therapy in acute coronary syndrome: a network meta-analysis of 61 898 patients from 15 randomized trials. Eur Heart J. 2022;43(10):959-67.
5. Shah RR. Genotype-guided warfarin therapy: Still of only questionable value two decades on. Journal of clinical pharmacy and therapeutics. 2020;45(3):547-60.
6. Plumpton CO, Pirmohamed M, Hughes DA. Cost-Effectiveness of Panel Tests for Multiple Pharmacogenes Associated With Adverse Drug Reactions: An Evaluation Framework. Clinical Pharmacology & Therapeutics. 2019;105(6):1429-38.
7. Hughes DA. Economics of Pharmacogenetic-Guided Treatments: Underwhelming or Overstated? Clinical Pharmacology & Therapeutics. 2018;103(5):749-51.
8. Ginsburg GS, Cavallari LH, Chakraborty H, Cooper-DeHoff RM, Dexter PR, Eadon MT, et al. Establishing the value of genomics in medicine: the IGNITE Pragmatic Trials Network. Genet Med. 2021;23(7):1185-91.
9. van der Wouden CH, Cambon-Thomsen A, Cecchin E, Cheung KC, Dávila-Fajardo CL, Deneer VH, et al. Implementing Pharmacogenomics in Europe: Design and Implementation Strategy of the Ubiquitous Pharmacogenomics Consortium. Clin Pharmacol Ther. 2017;101(3):341-58.
10. Bousman CA, Bengesser SA, Aitchison KJ, Amare AT, Aschauer H, Baune BT, et al. Review and Consensus on Pharmacogenomic Testing in Psychiatry. Pharmacopsychiatry. 2021;54(1):5-17.
11. Bousman C, Arandjelovic K, Mancuso S, Eyre H, Dunlop D. Pharmacogenetic tests and depressive symptom remission: a meta-analysis of randomized controlled trials. Pharmacogenomics. 2019;20(1):37-47.
12. Relling MV, Evans WE. Pharmacogenomics in the clinic. Nature. 2015;526(7573):343-50.
13. Abdullah-Koolmees H, van Keulen AM, Nijenhuis M, Deneer VHM. Pharmacogenetics Guidelines: Overview and Comparison of the DPWG, CPIC, CPNDS, and RNPGx Guidelines. Front Pharmacol. 2021;11:1-12.
14. Whirl-Carrillo M, Huddart R, Gong L, Sangkuhl K, Thorn CF, Whaley R, et al. An Evidence-Based Framework for Evaluating Pharmacogenomics Knowledge for Personalized Medicine. Clinical Pharmacology & Therapeutics. 2021;110(3):563-72.
15. Reis-Pardal J, Rodrigues A, Rodrigues E, Fernandez-Llimos F. Comparing cytochrome P450 pharmacogenetic information available on United States drug labels and European Union Summaries of Product Characteristics. The pharmacogenomics journal. 2017;17(6):488-93.
16. Koutsilieri S, Tzioufa F, Sismanoglou D-C, Patrinos GP. Unveiling the guidance heterogeneity for genome-informed drug treatment interventions among regulatory bodies and research consortia. Pharmacological research. 2020;153:104590.
17. Cacabelos R, Cacabelos N, Carril JC. The role of pharmacogenomics in adverse drug reactions. Expert Rev Clin Pharmacol. 2019;12(5):407-42.
18. Rosenman MB, Decker B, Levy KD, Holmes AM, Pratt VM, Eadon MT. Lessons Learned When Introducing Pharmacogenomic Panel Testing into Clinical Practice. Value Health. 2017;20(1):54-9.
19. Hall A, Payne S. What is the IVDR? - briefing. PHG Foundation, University of Cambridge, UK,; 2018.

20. Murphy LE, Fonseka TM, Bousman CA, Müller DJ. Gene-drug pairings for antidepressants and antipsychotics: level of evidence and clinical application. Mol Psychiatry. 2021;27:593-605.
21. The Royal College of Pathologists of Australasia. Utilisation of pharmacogenetics in healthcare. Surry Hills, NSW, Australia.; 2018.
22. Nagaraj S, Toombs M. The Gene-Drug Duality: Exploring the Pharmacogenomics of Indigenous Populations. Frontiers in genetics. 2021;12:1-6.
23. Royal College of Physicians, British Pharmacological Society. Personalised prescribing: using pharmacogenomics to improve patient outcomes: Report of a working party. London: RCP and BPS; 2022.
24. Magavern EF, Daly AK, Gilchrist A, Hughes D. Pharmacogenomics spotlight commentary: From the United Kingdom to global populations. Br J Clin Pharmacol. 2021:1-3.
25. Australian Genomics. Preliminary Implementation Recommendations: A national approach to genomic information management. 2022 April.
26. Turner RM, Magavern EF, Pirmohamed M. Pharmacogenomics: Relevance and opportunities for clinical pharmacology. Br J Clin Pharmacol. 2022:1-3.
27. Krebs K, Milani L. Translating pharmacogenomics into clinical decisions: do not let the perfect be the enemy of the good. Human genomics. 2019;13(1):1-13.
28. Zanardi R, Prestifilippo D, Fabbri C, Colombo C, Maron E, Serretti A. Precision psychiatry in clinical practice. International Journal of Psychiatry in Clinical Practice. 2021;25(1):19-27.
29. Hayward J, McDermott J, Qureshi N, Newman W. Pharmacogenomic testing to support prescribing in primary care: a structured review of implementation models. Pharmacogenomics. 2021;22(12):761-76.
30. Dunnenberger HM, Crews KR, Hoffman JM, Caudle KE, Broeckel U, Howard SC, et al. Preemptive clinical pharmacogenetics implementation: current programs in five US medical centers. Annual review of pharmacology and toxicology. 2015;55:89-106.
31. Turner RM, Newman WG, Bramon E, McNamee CJ, Wong WL, Misbah S, et al. Pharmacogenomics in the UK National Health Service: opportunities and challenges. Pharmacogenomics. 2020;21(17):1237-46.
32. van der Wouden CH, Paasman E, Teichert M, Crone MR, Guchelaar H-J, Swen JJ. Assessing the implementation of pharmacogenomic panel-testing in primary care in the Netherlands utilizing a theoretical framework. J Clin Med. 2020;9(3):814.
33. Subasri M, Barrett D, Sibalija J, Bitacola L, Kim RB. Pharmacogenomic-based personalized medicine: Multistakeholder perspectives on implementational drivers and barriers in the Canadian healthcare system. Clinical and translational science. 2021;14(6):2231-41.
34. Swen JJ, Nijenhuis M, van Rhenen M, de Boer-Veger NJ, Buunk AM, Houwink EJ, et al. Pharmacogenetic information in clinical guidelines: the European perspective. Clinical Pharmacology & Therapeutics. 2018;103(5):795-801.
35. Ang HX, Chan SL, Sani LL, Quah CB, Brunham LR, Tan BOP, et al. Pharmacogenomics in Asia: a systematic review on current trends and novel discoveries. Pharmacogenomics. 2017;18(9):891-910.
36. Dandara C, Masimirembwa C, Haffani YZ, Ogutu B, Mabuka J, Aklillu E. African Pharmacogenomics Consortium: Consolidating pharmacogenomics knowledge, capacity development and translation in Africa [version 1; peer review: 2 approved]. AAS Open Res. 2019;2:19.
37. Suarez-Kurtz G, Aklillu E, Saito Y, Somogyi AA. Conference report: pharmacogenomics in special populations at WCP2018. British Journal of Clinical Pharmacology. 2019;85(3):467-75.
38. Tillman E, Beavers C, Afanasjeva J. Current and future state of clinical pharmacist-led precision medicine initiatives. Journal of the Amerian College of Clinical Pharmacy. 2021;4:754-64.

39. Zanardi R, Manfredi E, Montrasio C, Colombo C, Serretti A, Fabbri C. Pharmacogenetic-Guided Treatment of Depression: Real-World Clinical Applications, Challenges, and Perspectives. Clinical Pharmacology & Therapeutics. 2021;110(3):573-81.
40. Ramsey LB, Prows CA, Zhang K, Saldaña SN, Sorter MT, Pestian JP, et al. Implementation of pharmacogenetics at Cincinnati Children's Hospital Medical Center: lessons learned over 14 years of personalizing medicine. Clin Pharmacol Ther. 2019;105(1):49-52.
41. Bell GC, Crews KR, Wilkinson MR, Haidar CE, Hicks JK, Baker DK, et al. Development and use of active clinical decision support for preemptive pharmacogenomics. J Am Med Inform Assoc. 2014;21(e1):e93-9.
42. van der Wouden CH, Bank PC, Özokcu K, Swen JJ, Guchelaar H-J. Pharmacist-initiated pre-emptive pharmacogenetic panel testing with clinical decision support in primary care: record of PGx results and real-world impact. Genes. 2019;10(6):416.
43. Papastergiou J, Quilty LC, Li W, Thiruchselvam T, Jain E, Gove P, et al. Pharmacogenomics guided versus standard antidepressant treatment in a community pharmacy setting: A randomized controlled trial. Clinical and translational science. 2021;14(4):1359-68.
44. Matey ET, Ragan AK, Oyen LJ, Vitek CR, Aoudia SL, Ragab AK, et al. Nine-gene pharmacogenomics profile service: The Mayo Clinic experience. Pharmacogenomics J. 2021;22:69-74.
45. Mostafa S, Polasek TM, Sheffield LJ, Huppert D, Kirkpatrick CMJ. Quantifying the Impact of Phenoconversion on Medications With Actionable Pharmacogenomic Guideline Recommendations in an Acute Aged Persons Mental Health Setting. Frontiers in Psychiatry. 2021;12.
46. Kisor DF, Petry NJ, Bright DR. Pharmacogenomics in the United States Community Pharmacy Setting: The Clopidogrel-CYP2C19 Example. Pharmacogenomics and personalized medicine. 2021;14:569-77.
47. Owusu-Obeng A, Weitzel KW, Hatton RC, Staley BJ, Ashton J, Cooper-Dehoff RM, et al. Emerging roles for pharmacists in clinical implementation of pharmacogenomics. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2014;34(10):1102-12.
48. Volpi S, Bult CJ, Chisholm RL, Deverka PA, Ginsburg GS, Jacob HJ, et al. Research directions in the clinical implementation of pharmacogenomics: an overview of US programs and projects. Clinical Pharmacology & Therapeutics. 2018;103(5):778-86.
49. Hoffman JM, Haidar CE, Wilkinson MR, Crews KR, Baker DK, Kornegay NM, et al. PG4KDS: a model for the clinical implementation of pre-emptive pharmacogenetics. Am J Med Genet C Semin Med Genet. 2014;166c(1):45-55.
50. Weinstein S, Carroll JC, Jukic S, Mcgivney MS, Klatt P. Perspectives of a pharmacist-run pharmacogenomic service for depression in interdisciplinary family medicine practices. Journal of the American College of Clinical Pharmacy. 2020;3(2):417-24.
51. Levy KD, Wu RR, Goto D, Ramos MA, Pratt VM, Hicks JK, et al. Translating pharmacogenetics from research to routine clinical practice–a survey of the IGNITE Network. Translational Medicine Communications. 2020;5(1):1-9.
52. Zhou Y, Krebs K, Milani L, Lauschke VM. Global frequencies of clinically important HLA alleles and their implications for the cost-effectiveness of preemptive pharmacogenetic testing. Clinical Pharmacology & Therapeutics. 2021;109(1):160-74.
53. Arwood MJ, Chumnumwat S, Cavallari LH, Nutescu EA, Duarte JD. Implementing pharmacogenomics at your institution: establishment and overcoming implementation challenges. Clinical and translational science. 2016;9(5):233-45.
54. van der Wouden CH, van Rhenen MH, Jama WO, Ingelman-Sundberg M, Lauschke VM, Konta L, et al. Development of the PG x-Passport: A Panel of Actionable Germline Genetic Variants for Pre-Emptive Pharmacogenetic Testing. Clinical Pharmacology & Therapeutics. 2019;106(4):866-73.

55. Liu M, Vnencak-Jones CL, Roland BP, Gatto CL, Mathe JL, Just SL, et al. A tutorial for pharmacogenomics implementation through end-to-end clinical decision support based on ten years of experience from PREDICT. Clinical Pharmacology & Therapeutics. 2021;109(1):101-15.
56. Bousman CA, Jaksa P, Pantelis C. Systematic evaluation of commercial pharmacogenetic testing in psychiatry: a focus on CYP2D6 and CYP2C19 allele coverage and results reporting. Pharmacogenet Genomics. 2017;27(11):387-93.
57. Thase ME, Parikh SV, Rothschild AJ, Dunlop BW, DeBattista C, Conway CR, et al. Impact of Pharmacogenomics on Clinical Outcomes for Patients Taking Medications With Gene-Drug Interactions in a Randomized Controlled Trial. J Clin Psychiatry. 2019;80(6).
58. Kim K, Magness JW, Nelson R, Baron V, Brixner DI. Clinical Utility of Pharmacogenetic Testing and a Clinical Decision Support Tool to Enhance the Identification of Drug Therapy Problems Through Medication Therapy Management in Polypharmacy Patients. J Manag Care Spec Pharm. 2018;24(12):1250-9.
59. Elliott LS, Henderson JC, Neradilek MB, Moyer NA, Ashcraft KC, Thirumaran RK. Clinical impact of pharmacogenetic profiling with a clinical decision support tool in polypharmacy home health patients: A prospective pilot randomized controlled trial. PLoS One. 2017;12(2):e0170905.
60. Franks PW, Melén E, Friedman M, Sundström J, Kockum I, Klareskog L, et al. Technological readiness and implementation of genomic-driven precision medicine for complex diseases. J Intern Med. 2021;290(3):602-20.
61. Brixner D, Biltaji E, Bress A, Unni S, Ye X, Mamiya T, et al. The effect of pharmacogenetic profiling with a clinical decision support tool on healthcare resource utilization and estimated costs in the elderly exposed to polypharmacy. Journal of medical economics. 2016;19(3):213-28.
62. Hinderer M, Boeker M, Wagner SA, Lablans M, Newe S, Hülsemann JL, et al. Integrating clinical decision support systems for pharmacogenomic testing into clinical routine-a scoping review of designs of user-system interactions in recent system development. BMC medical informatics and decision making. 2017;17(1):1-14.
63. Haidar CE, Relling MV, Hoffman JM. Preemptively Precise: Returning and Updating Pharmacogenetic Test Results to Realize the Benefits of Preemptive Testing. Clinical Pharmacology & Therapeutics. 2019;106(5):942-4.
64. Bank PC, Swen JJ, Guchelaar H-J. A nationwide survey of pharmacists' perception of pharmacogenetics in the context of a clinical decision support system containing pharmacogenetics dosing recommendations. Pharmacogenomics. 2017;18(3):215-25.
65. Herr TM, Bielinski SJ, Bottinger E, Brautbar A, Brilliant M, Chute CG, et al. Practical considerations in genomic decision support: The eMERGE experience. Journal of pathology informatics. 2015;6.
66. Sukasem C, Jantararoungtong T, Koomdee N. Pharmacogenomics research and its clinical implementation in Thailand: Lessons learned from the resource-limited settings. Drug Metabolism and Pharmacokinetics. 2021;39:100399.
67. Youssef E, Kirkdale CL, Wright DJ, Guchelaar HJ, Thornley T. Estimating the potential impact of implementing pre-emptive pharmacogenetic testing in primary care across the UK. Br J Clin Pharmacol. 2021;87:2907–25.
68. Karas Kuželički N, Prodan Žitnik I, Gurwitz D, Llerena A, Cascorbi I, Siest S, et al. Pharmacogenomics education in medical and pharmacy schools: conclusions of a global survey. Pharmacogenomics. 2019;20(9):643-57.
69. Just KS, Turner RM, Dolžan V, Cecchin E, Swen JJ, Gurwitz D, et al. Educating the next generation of pharmacogenomics experts: global educational needs and concepts. Clinical pharmacology and therapeutics. 2019;106(2):313-6.

70. Caspar SM, Schneider T, Stoll P, Meienberg J, Matyas G. Potential of whole-genome sequencing-based pharmacogenetic profiling. Pharmacogenomics. 2021;22(03):177-90.
71. Frueh FW. Real-world clinical effectiveness, regulatory transparency and payer coverage: three ingredients for translating pharmacogenomics into clinical practice. Pharmacogenomics. 2010;11(5):657-60.
72. Osanlou O, Pirmohamed M, Daly AK. Chapter Seven - Pharmacogenetics of adverse drug reactions. Brøsen K, Damkier P, editors: Academic Press; 2018.
73. Manson LEN, Swen JJ, Guchelaar H-J. Diagnostic Test Criteria for HLA Genotyping to Prevent Drug Hypersensitivity Reactions: A Systematic Review of Actionable HLA Recommendations in CPIC and DPWG Guidelines. Front Pharmacol. 2020;11.
74. Grosse SD, Khoury MJ. What is the clinical utility of genetic testing? Genetics in Medicine. 2006;8(7):448-50.
75. Smart A. A multi-dimensional model of clinical utility. International Journal for Quality in Health Care. 2006;18(5):377-82.
76. Moorthie S, Harris J. Clinical utility. PHG Foundation: University of Cambridge; 2021.
77. Relling M, Klein T. CPIC: clinical pharmacogenetics implementation consortium of the pharmacogenomics research network. Clinical Pharmacology & Therapeutics. 2011;89(3):464-7.
78. Verbelen M, Weale ME, Lewis CM. Cost-effectiveness of pharmacogenetic-guided treatment: are we there yet? The pharmacogenomics journal. 2017;17(5):395-402.
79. Singh DB. The Impact of Pharmacogenomics in Personalized Medicine. Adv Biochem Eng Biotechnol. 2020;171:369-94.
80. Berm EJ, Looff Md, Wilffert B, Boersma C, Annemans L, Vegter S, et al. Economic evaluations of pharmacogenetic and pharmacogenomic screening tests: a systematic review. Second update of the literature. PloS one. 2016;11(1):e0146262.
81. David V, Fylan B, Bryant E, Smith H, Sagoo GS, Rattray M. An Analysis of Pharmacogenomic-Guided Pathways and Their Effect on Medication Changes and Hospital Admissions: A Systematic Review and Meta-Analysis. Front Genet. 2021;12:698148.
82. Kloypan C, Koomdee N, Satapornpong P, Tempark T, Biswas M, Sukasem C. A Comprehensive Review of HLA and Severe Cutaneous Adverse Drug Reactions: Implication for Clinical Pharmacogenomics and Precision Medicine. Pharmaceuticals. 2021;14:1077.
83. Li KX, Loshak H. Pharmacogenomic testing in depression: a review of clinical effectiveness, cost-effectiveness, and guidelines (CADTH rapid response report: summary with critical appraisal). Ottawa: CADTH; 2020.
84. Carrascal-Laso L, Franco-Martín MÁ, Marcos-Vadillo E, Ramos-Gallego I, García-Berrocal B, Mayor-Toranzo E, et al. Economic Impact of the Application of a Precision Medicine Model (5SPM) on Psychotic Patients. Pharmacogenomics and Personalized Medicine. 2021;14:1015-25.
85. Rosenblat JD, Lee Y, McIntyre RS. The effect of pharmacogenomic testing on response and remission rates in the acute treatment of major depressive disorder: a meta-analysis. Journal of affective disorders. 2018;241:484-91.
86. Ielmini M, Caselli I, Critelli F, Mattia M, Bellini A, Callegari C. Efficacy and tolerability of therapies set under pharmacogenetic tools suggestions: A systematic review with meta-analysis about mood disorders. Psychiatry Research. 2022;311:114482.
87. Marshe VS, Islam F, Maciukiewicz M, Bousman C, Eyre HA, Lavretsky H, et al. Pharmacogenetic Implications for Antidepressant Pharmacotherapy in Late-Life Depression: A Systematic Review of the Literature for Response, Pharmacokinetics and Adverse Drug Reactions. Am J Geriatr Psychiatry. 2020;28(6):609-29.
88. Zhu Y, Swanson KM, Rojas RL, Wang Z, Sauver JLS, Visscher SL, et al. Systematic review of the evidence on the cost-effectiveness of pharmacogenomics-guided treatment for cardiovascular diseases. Genetics in Medicine. 2020;22(3):475-86.

89. Wu Y, Zhou Y, Pan Y, Zhao X, Liu L, Wang D, et al. Impact of CYP2C19 polymorphism in prognosis of minor stroke or TIA patients with declined eGFR on dual antiplatelet therapy: CHANCE substudy. Pharmacogenomics J. 2018;18(6):713-20.
90. Chora JR, Bourbon M. Pharmacogenomics of statins and familial hypercholesterolemia. Current Opinion in Lipidology. 2021;32(2):96-102.
91. White C, Scott RJ, Paul C, Ziolkowski A, Mossman D, Fox SB, et al. Dihydropyrimidine Dehydrogenase Deficiency and Implementation of Upfront DPYD Genotyping. Clinical Pharmacology & Therapeutics. 2022:1-12.
92. O'Shea J, Ledwidge M, Gallagher J, Keenan C, Ryan C. Pharmacogenetic interventions to improve outcomes in patients with multimorbidity or prescribed polypharmacy: a systematic review. The Pharmacogenomics Journal. 2022;22(2):89-99.
93. Maciel A, Cullors A, Lukowiak AA, Garces J. Estimating cost savings of pharmacogenetic testing for depression in real-world clinical settings. Neuropsychiatric disease and treatment. 2018;14:225–30.
94. Bank P, Swen J, Guchelaar H. Estimated nationwide impact of implementing a preemptive pharmacogenetic panel approach to guide drug prescribing in primary care in The Netherlands. BMC medicine. 2019;17(1):1-14.
95. Amara N, Blouin-Bougie J, Bouthillier D, Simard J. On the readiness of physicians for pharmacogenomics testing: an empirical assessment. The pharmacogenomics journal. 2018;18(2):308-18.
96. Overby CL, Erwin AL, Abul-Husn NS, Ellis SB, Scott SA, Obeng AO, et al. Physician attitudes toward adopting genome-guided prescribing through clinical decision support. Journal of personalized medicine. 2014;4(1):35-49.
97. Thomas CD, Parvataneni HK, Gray CF, Deen JT, Prieto HA, Pulido LF, et al. A hybrid implementation-effectiveness randomized trial of CYP2D6-guided postoperative pain management. Genet Med. 2021;23(4):621-8.
98. Peterson JF, Field JR, Unertl K, Schildcrout JS, Johnson DC, Shi Y, et al. Physician response to implementation of genotype-tailored antiplatelet therapy. Clinical Pharmacology & Therapeutics. 2016;100(1):67-74.
99. Hendricks-Sturrup RM, Linsky A, Lu CY, Vassy JL. Genomic testing is best integrated into clinical practice when it is actionable. Personalized Medicine. 2020;17(1):5-8.
100. Freund CL, Wilfond BS. Emerging ethical issues in pharmacogenomics. American Journal of Pharmacogenomics. 2002;2(4):273-81.
101. Nuffield Council on Bioethics. Pharmacogenetics: ethical issues. London; 2006.
102. Luczak T, Stenehjem D, Brown J. Applying an equity lens to pharmacogenetic research and translation to under-represented populations. Clinical and translational science. 2021;14(6):2117-23.
103. Meli BA, Fenech AG, Cordina M, Agius E. Ethical aspects pertaining to the use of pharmacogenetic tests. Research in Social and Administrative Pharmacy. 2021;17(4):799-804.
104. Johnson D, Wilke MA, Lyle SM, Kowalec K, Jorgensen A, Wright GE, et al. A systematic review and analysis of the use of polygenic scores in pharmacogenomics. Clinical Pharmacology & Therapeutics. 2022;111(4):919-30.
105. Bellon T, Raymond N. Bristol-Myers, Sanofi Ordered to Pay Hawaii $834 Million Over Plavix Warning Label. US News and World Report. 2021 15Feb.
106. Zarkhin F. OHSU to pay $1 million, promises change to settle lawsuit from widow of cancer patient. The Oregonian. 2022 04May;Sect. Health.

APPENDICES

Appendix 1. Overview of the key database and clinical guidance organisations

Guidelines organisation	Role
Pharmacogene Variation Consortium (PharmVar)	Standardises nomenclature, catalogues pharmacogenic variation for test design and reporting.
Clinical Pharmacogenetics Implementation Consortium (CPIC®) https://cpicpharmacogenomics.org/guidelines/	Produces clinical guidelines for a patient's genotype or predicted phenotype. Aims to provide guidelines usable for practitioners even when they have not ordered test themselves.
Pharmacogenomics Knowledge Base (PharmGKB)	Collects and curates knowledge from CPIC, DPWG, CPNDS and drug labels with pharmacogenomics information from FDA, EMA, Swiss, Japan, Canada
Dutch Pharmacogenetic Working Group (DPWG)	First to publish guidelines (2005), includes recommendations in G-Standaard (Dutch drug database)
French National Network (Réseau) of Pharmacogenetics (RNPGx)	National guidelines and recommendations for when to test.
Canadian Pharmacogenomics Network for Drug Safety (CPNDS)	National guidelines and active surveillance network across Canada to follow up patients who have experienced ADRs and maintain database of phenotypic data.

Appendix 2. Pharmacogenomics networks and consortiums

Implementation Initiative	Key reference /url	Aim/ purpose	Who to test?	What to test?	When to test?
North America					
Implementing genomics in practice (IGNITE) Pragmatic Clinical Trials Network	https://doi.org/10.1186/s12920-015-0162-5	Pragmatic implementation trials in diverse settings and populations	African Americans and hypertension (n=5435), Pain and depression (n=4509)	APOL1 status, CYP2D6 and CYP2C19; Hypertension management pain (acute and chronic) depression	Reactive
Pharmacogenomics Research Network Translational Pharmacogenetics Program	https://doi.org/10.1002/cpt.630	Implementation assessment		Drug-gene pairs	Pre-emptive and at point-of-care
Indiana Genomics Implementation (INGENEOUS)	https://doi.org/10.1016/j.jval.2016.08.727	RCT	Underserved pops (n=6000, 2000 PGx and 4000 control)	Panel (14 gene, 43 variants 27/28 meds)	
Pharmacogenomics Resource for Enhanced Decisions in Care and Treatment (PREDICT)	https://doi.org/10.1002/cpt.2079	Develop framework for PGX in EHR		Panel (34 variants)	Pre-emptive
CLIPMERGE -PGx Electronic Medical Records and Genomics (eMERGE)-PGx project.	https://doi:10.1038/clpt.2013.72	Establish infrastructure	Biobank derived cohort (n=1500)	Panel (36 variants)	Pre-emptive

eMERGE (electronic medical records and genomics)	https://doi:10.1038/clpt.2013.59	Translational - Process and clinical outcomes.	Likely to be prescribed drug of interest in next 1-3 years (n=9000)	Panel (84 pharmacogenes)	Pre-emptive
PG4KDS	https://doi:10.1002/ajmg.c.31391	Implement to migrate tests into routine care	Paediatric (n=1559)	Panel (230 genes, 12 drugs)	Pre-emptive
Right Drug, Right Dose, Right Time (RIGHT) project Mayo	https://doi.org/10.1016/j.mayocp.2013.10.021	Translational - develop best practice for integrate PGx and CDS into EHR	Mayo Biobank patients	Panel (84 pharmacogenes)	Pre-emptive
1200 Patients Project	https://doi:10.1038/clpt.2012.117	Observation, implementation	Patients at high risk of ADRs or non-response	Panel (drugs with clinical evidence)	Pre-emptive
Personalized Medication Program	https://doi.org/10.2217/pgs.13.59	Implementation		HLA-B*1502-abacavir and TPMT-thiopurines	Pre-emptive
The Individualized Medicine: Pharmacogenetics Assessment and Clinical Treatment (IMPACT) project	https://doi.org/10.1016/j.jpsychires.2017.09.002	Implementation and evidence of effectiveness	Mental health patients	Panel (8 genes)	

Europe and UK

Ubiquitous Pharmacogenomics Consortium (U-PGx)	www.upgx.eu	Address challenges to implementation across Europe

PREemptive Pharmacogenomic testing for prevention of Adverse drug REactions (PREPARE) study - U-PGx	https://doi:10.1002/cpt.602	Evidence for reduced ADRs and efficacy	Current med users (n=8100, 4050 intervention and control)	Panel (clinically relevant markers where DPWG guidelines exist 43 drugs)	At first prescription of an index drug
The UK Pharmacogenetics and Stratified Medicine Network	https://precisionmedicineuk.com/home	Portal for information			
Africa					
African Pharmacogenomics Consortium (since 2018)	https://doi: 10.12688/aasopenres.12965.1	To consolidate African pharmacogenomics knowledge, capacity development and translation			
Asia					
South-East Asian Pharmacogenomics Research Network (SEAPharm)	https://doi: 10.1159/000502916	Pharmacogenomics implementation in Asian region			

Appendix 3. Medical Research Future Fund (MRFF) Strategic objectives

The Australian Medical Research and Innovation Strategy 2021-2026 (ref) lists the Strategic Objectives of the MRFF.

To deliver:

- *Equitable health outcomes through research-informed preventive health and health care across the spectrum from primary to tertiary care.*
- *Health and economic benefits from transformative and innovative research through translation of outcomes into policy and practice, and commercialisation of new diagnostics, therapeutics, and preventive health interventions.*
- *A skilled and sustainable health and medical research workforce with expertise in research translation, innovation, and commercialisation.*
- *A health and medical research sector and health system positioned to respond to emerging and future challenges.*

***Guiding principles** to support the strategy. Research funded through the MRFF will address:*

- *New or emerging areas of health need with high potential for generating innovative approaches, tools, or technologies to transform health care and practices.*
- *Existing areas of unmet health need, to address underinvestment and support capacity development with a focus on achieving equity in health outcomes, particularly for Aboriginal and Torres Strait Islander people and other priority populations.*
- *Improvement in the efficiency and effectiveness of the health system, by promoting adoption of evidence-based practices, enabling equitable health outcomes, and focussing on the needs of patients, their families, and carers.*
- *Social, environmental, and cultural factors that impact health and wellbeing, including strengths-based approaches that leverage patient/consumer and community knowledge and experience to deliver improvements in population health and wellbeing.*
- *Enhancements to the translation of research outputs to deliver impact through health and economic outcomes, including through commercialisation of research outcomes and implementation of policy changes nationally and globally.*
- *Promotion of capacity and capability in the health and medical research workforce, through investments in priority areas, by fostering collaboration between research groups and across disciplines and addressing gender equity.*
- *Encouragement of adaptive approaches to emerging challenges, supporting rapid response and effective collaboration both nationally and internationally with other public and private sources of health and medical research funding.*

Appendix 4. National consultation Stage 2 - stakeholder survey

Pharmacogenomics Incubator Project - Opportunity to Review and Feedback on Stakeholder Interviews

Background

Pharmacogenomics Incubator Project

The incubator project model, part of Australian Genomics Grant Program (2021 – 2023), was proposed to develop health genomic research priority areas considered to be of strategic importance to Australia, but that are either too immature for large scale funding, or risk a fragmented collection of submissions to a competitive call. It is for areas considered time-critical to advance Australian genomic research strategy, and clinical translation.

AIM

To identify the research priority areas around pharmacogenomic testing for quality use of medicine in the Australia healthcare system.

Methods

National consultation conducted in 3 stages:

- Stage 1 (Oct21 – Mar22) – identify key stakeholders for individual interviews. Explore Australia's current pharmacogenomics practice, current and future barriers to expanding testing and how they might be overcome, specific gaps that need addressing, and what a future research collaboration could achieve if funded. Interview data analysed to develop recommendations.
- Stage 2 (this survey) – online survey to review and receive feedback on recommendations from Stage 1. Responses will inform final report.
- Stage 3 - circulate final draft report for comment.

Summary of findings from interviews with stakeholders (Stage 1)

The current state of pharmacogenomics in Australia:

- Number of providers offering services is increasing, including direct-to-consumer.
- Number of tests conducted is low (both publicly and privately funded)
- Medical Benefits Scheme (MBS) funding is available for two tests.
- Turnaround times long, up to 3 weeks.
- TGA defines all tests as moderate to high risk (Class 3 in-vitro medical devices).
- Little local evidence of cost-effectiveness and clinical utility, unknown which patients and populations have highest value.
- Australian genetic reference data limited, Indigenous pharmacogenes mostly unknown.
- Knowledge and awareness among practitioners poor, workforce unprepared.
- Evidence-based models of service not developed (most testing is lone physician).
- No standards-based options for storing and accessing reports, sharing across jurisdictions, or integrating with clinical decision support.
- Research activity siloed in small trials and single-site hospital settings, little practice change post-trial.
- Few clinical champions and little political will to break status quo.

Key recommendations for Australia:

- Expand pharmacogenomic testing where there is evidence to improve quality use of medicines.
- Form a national steering network with individual and organisational representation for cross sector coordination and leadership.

- Research testing in routine practice for cost effectiveness and utility evidence; identify populations, therapeutic areas and contexts with greatest benefit.
- Develop local clinical protocols using international guidelines, international implementation exemplars and local evidence.
- Integrate pharmacogenomic clinical protocols into existing quality use of medicine practices and non-genetic clinical protocols (not standalone tool); include indications for testing, and therapeutic options for potential results, guidance for laboratories on how/what to report.
- Develop models of pharmacogenomic testing services with practitioner roles and standards of consent and reporting.
- Secure MBS funding.
- Build practitioner knowledge through training/ education (tertiary level and practitioner development)
- Develop supporting IT infrastructure - electronic health records, interfaces, clinical decision support tools (data storage, access, privacy, and reinterpretation capacity)
- Improve Australian pharmacogenomic reference data to include Indigenous populations and ethnic diversity.

Research priorities

1. **Implementation research**
2. **Models of practice**
3. **Education**

There is an opportunity to provide feedback on the research priorities in the following pages.

Priority 1 – Implementation Research

International experience and evidence provide rich guidance for local implementation. Limits to its generalisability arise from differences in healthcare systems and local healthcare environments. Drug prices, test prices, formularies and prescribing habits differ. Australia requires local studies for pharmacogenomic testing to demonstrate utility and cost-effectiveness, to understand experience of patients and practitioners, and to explore unintended consequences.

Despite up to ninety nine percent of individuals having an 'actionable' drug-gene variant, most will not benefit from a test. We need to identify populations who will have the greatest clinical benefit and economic value, meaning fewer people need to be tested to find one with the variant of concern. They can be identified by drug, therapeutic area, ethnicity or context.

Pragmatic study designs are needed in real world contexts for assessing benefit and cost-effectiveness of pharmacogenomics testing. Real-world variables include non-genetic inter-individual response to medications and the adherence of practitioners to recommendations and patients to medications. The gold standard for collecting evidence in healthcare, the randomised controlled trial, may not be feasible or appropriate. Researchers need to consider appropriate endpoints for assessment. Clinical and social benefits can occur months or years post-test (perhaps long after a trial has completed reporting).

What to test for needs evidence, consensus and funding. Multi-gene panel testing for preventing adverse drug reactions and improving medication efficacy have lifelong utility. They are now of similar cost to single drug-gene tests: economic modelling suggests cost effectiveness is higher for panels over

single gene tests. Some drug targets from early studies have been superseded by alternative drugs with less genetic variability (e.g. clopidogrel), or an objective phenotypic test embedded in practice protocols (e.g. warfarin).

Potential indications for pharmacogenomics testing:

- Rare HLA genetic variants associated with serious or life-threatening adverse events (e.g. allopurinol, carbamazepine, phenytoin). Cost benefit analysis to consider social and ethical domains.
- High risk medicines.
- Polypharmacy (10th national health priority) – some evidence can reduce hospital stays and emergency department visits.
- Conditions where drug response critical (e.g. immunosuppressants to prevent transplant rejection).
- Psychiatry – genetic variants cause different patient responses to medications (metabolism of cypP450 2C19 and 2D6 are subject to genetic variation). Evidence is strongest for individuals with moderate to severe depression, and a previous adverse effect or poor efficacy. Pre-emptive testing for initial medication response is unknown (the likelihood of benefit and/or remission).

Australian pharmacogenomic reference data needs to represent Indigenous populations and non-European diversity. It would benefit from systematic follow up of adverse drug reactions inclusive of pharmacogenomics testing.

The recommendation for implementation research is:

That research be conducted to better understand pharmacogenomic testing to guide quality use of medicines, focusing on:

b. the benefits, harms and value (cost-effectiveness), and the circumstances relating to setting of care, testing strategy and therapeutic area;
c. the limitations and potential unintended consequences of testing, including ethical, legal, privacy and social aspects;
d. the experiences of patients and practitioners.

Studies will:

- *include Australia's population diversity (Indigenous and ethnicities underrepresented in European dominated reference data that informs international guidelines).*
- *promote equity in testing (geographic and socioeconomic access).*
- *consider pragmatic designs across various 'real world' contexts.*
- *build workforce capacity for testing.*

Population cohorts and indications with potential benefit (higher value) include:

a. Candidates for drugs with known HLA hypersensitivity genes (and family members) (test proactively, prior to prescribing)
b. Individuals currently taking a drug with high level pharmacogenetic evidence who have had an adverse drug event or lack of efficacy (test reactively to improve medication safety and efficacy, and to inform adverse event reporting databases)
c. Individuals being initiated on a drug with high level pharmacogenetic evidence where it is recommended in a clinical protocol and/or by a pharmacogenomic pharmacist (test proactively to improve medication safety and efficacy).

d. Individuals taking polypharmacy inclusive of a drug with high level pharmacogenetic evidence where it is the recommendation of a medication review pharmacist (test reactively to improve medication safety and efficacy)
e. Individuals prescribed a drug where inadequate drug response could result in significant morbidity and mortality (e.g. anti-rejection medicines in transplantation)

Feedback questions

Question 1. Do the recommendations for research represent your view of the priorities for Australia regarding implementation of pharmacogenomics? [yes/no; comment]
Question 2. Are the potential population cohorts identified appropriate research priorities?
a. candidates for drugs linked to HLA genes, [yes/no; comment]
b. following an adverse event, [yes/no; comment]
c. at initiation of a drug with high level evidence [yes/no; comment].
d. in polypharmacy with a medication review pharmacist recommendation [yes/no; comment]and,
e. inadequate drug response a potential risk [yes/no; comment].
Question 3. Further comments (free text)

Priority 2 – Models of Practice

Models of service for testing require collaboration between patients and healthcare professionals (such as prescribers, pharmacologists, pharmacists and laboratory scientists). Evidence suggests collaboration is both feasible and valued. The literature has little consensus on service models and it remains unclear which practitioners are most suited for each role . Models to be informed by local context and be prepared to evolve as needed.

Key processes and roles in pharmacogenomics programs performed by patient facing practitioners include: pre-test counselling and consent; test ordering; interpretation of the results with non-genetic information and relevant clinical guidelines; presentation of reports with recommendations; and post-test counselling and shared decision making with the patient.

The resources currently used by practitioners contain little pharmacogenomic information and guidance (TGA approved product information from sponsors, The Australian Medicines Handbook, Therapeutic Guidelines, MIMs, the National Prescribing Service and discipline specific guidance from professional bodies and specialties). Guidance with pharmacogenomic information proactively informs prescribing decisions, and reactively informs actions in event of medication harm. Knowledge and protocols should be at hand to ensure practitioners question whether a genetic factor is responsible and if a test available.

Clinical decision support is vital to utility and successful uptake of testing. It requires integration into practice software (that is, prescribing and dispensing software) for ready access to support treatment decisions at the point of care.

The recommendation is:
Conduct research to develop and evaluate models of practice of pharmacogenomic testing with collaboration between healthcare professionals (including prescribers, pharmacists, laboratory scientists) and patients. The key lines of enquiry:

d. Defining the processes and roles for:
i. Pre-test patient counselling, consent and ordering of tests.
ii. Interpretation and recommendations for treatment using pharmacogenomic results, non-genetic patient information and clinical guidelines.
iii. Presentation of reports containing results and recommendations
iv. Shared decision making and post-test patient counselling.
e. *Digital health considerations that would see the integration of pharmacogenomics into the current electronic health records and clinical decision support tools.*

Feedback questions

Question 1. Does the priority to develop models of practice that are collaborative across health practitioners such as prescribers and pharmacists, with clear roles, reflect your view? [yes/no; comment]
Question 2. Are digital health considerations a research priority? [yes/no; comment]
Question 3. Further comments

Priority 3 - Education

A significant barrier to wider implementation of pharmacogenomic testing in practice is low level of practitioner knowledge, competence and confidence to order a test or understand a report if it were presented. Building capacity lessens the impact on the current healthcare workforce of predicted testing increases. With legal precedence having been established, practitioners without competence risk litigation.

Modules for pharmacogenomics need to be included in practitioner education through curriculum development in university degrees and professional development. Guidance can be taken from the US where it is a component of many pharmacy degrees and post-graduate certification is provided by several tertiary institutions.

Poor practitioner understanding of the foundational concepts of pharmacology should be acknowledged - pharmacodynamics and pharmacokinetics (absorption, distribution, metabolism and excretion of drugs (ADME)) and the cytochrome P450 enzymes which are involved in the majority of drug metabolization. Many will be challenged to interpret pharmacogenomic results and competently guide prescribing decisions. Collaboration includes knowing personal limits and gaining ready access to expertise.

The recommendation is:
Research to develop and evaluate national standards for education related to pharmacogenomics considering local needs and international exemplars:

e. university-level training
f. specialist training at the practitioner level
g. continuing professional development

Feedback questions

Question 1. Does the priority to develop and evaluate education for Australian institutions reflect your view? [yes/no; comment]
Question 2. Further comments

Appendix 5. Potential therapeutic areas for implementation (from national consultation interviews and survey)

What to test?	When to test?	What is purpose/ benefits?	What are risks?
HLA a and b - Carbamazepine - Allopurinol - Phenytoin - Vancomycin - Dapsone - Abacavir - Carbamazepine - Oxcarbazepine - Phenytoin - Allopurinol - Flucloxacillin - Lamotrigine	Prior to prescribing	To avoid exposure to medicines in patients with hypersensitivity allele (predict immunological response, adverse effect)	Prescribers avoid test due to perceived hassle/ lack of knowledge. Therapeutic options reduced or alternative medicines privileged.
Drugs in patient's current regimen with level 1A CPIC evidence (in a panel)	Reactively when an issue presents (along with/after medicine history, interactions, physiological and phenotypic measures) Pre-emptively Polypharmacy	To explore if genetics is a causative factor (confirm adverse effect). To guide current and future decisions.	Genetic data privileged over other physiological data and patient preferences. Therapeutic options are reduced or alternative medicines privileged. Expensive data storage.
Other examples (not exhaustive):			
Clopidogrel	Pre percutaneous coronary intervention (PCI)	To inform post intervention anti-platelet treatment.	Prescribers avoid test due to perceived hassle/ lack of knowledge. Therapeutic options reduced or alternative medicines privileged.
DPYD 5-fluorouracil, capecitabine	Before treatment	To identify DPD deficiency and minimise severe adverse reactions.	Prescribers avoid test due to perceived hassle/ lack of knowledge. Therapeutic options reduced or alternative medicines privileged.

			Poor clinical outcome from sub-therapeutic dosing.

Health professional steward	**For**	**Against**
Pharmacists (clinical)	- already have foundational pharmacology knowledge - skilled at medicine history/ review - Used to working in teams	- Limited access to patient data - Remuneration options limited.
General practice	- Prescribers with patient data access	- Time poor, most not willing - Limited foundational pharmacology knowledge - Primary care often not working in cross-disciplinary teams - Limited medication reconciliation skills/data access
Medical specialists	- See patients with issues and increased complexity	- Some specialties prefer using objective phenotypic measures - Limited foundational pharmacology knowledge -Limited medication reconciliation skills/data access
Clinical pharmacologist	- already have foundational pharmacology knowledge - skilled at phenotypic measures	- Few and time poor - Limited funding currently available