The Royal College of Pathologists of Australasia
ABN 52 000 173 231

Durham Hall 207 Albion Street Surry Hills NSW 2010 Australia
Telephone 61 2 8356 5858 Facsimile 61 2 8356 5828

RCPA
The Royal College of Pathologists of Australasia

Position Statement

Subject:	**Utilisation of pharmacogenetics in healthcare**
Approval Date:	July 2018
Review Date:	July 2022
Review By:	BPPQ
Number:	3 /2018

Summary

This position paper has been developed by representatives from a number of Australasian medical Colleges to describe the significance of genetic testing to predict a patient's response to drugs. The document is directed to healthcare professionals and to those developing policy for Australian healthcare although many of the principles apply equally to New Zealand.

1. Pharmacogenetics is the study of the interaction between medicinal drugs and a patient's genes. By using pharmacogenetic testing, a clinician can align a prescription with the patient's potential for a therapeutic or adverse response to the drug. This is a rapidly growing discipline in healthcare, and Australia is under-represented in the field.
2. Pharmacogenetics has potential application in most areas of healthcare. For patients in whom metabolism of a drug differs from the average, the appropriate response can vary from modifying the dose of the drug to selecting a drug that is metabolised by a different genetic pathway.
3. The substantiation and implementation of pharmacogenetics can be complicated by the subjectivity of patient symptoms, variations in drug metabolism caused by the disease and other therapies, and the interactions of multiple drugs, multiple genes, and the medical history of a patient.
4. A pharmacogenetic test result can modify the prescribing of drugs that are already approved for clinical use. Hence the threshold of evidence for a pharmacogenetic interpretation does not necessarily need to be as high as would be required for approval of a novel drug or care pathway. Australasian guidelines for clinical practice should adopt the evidentiary standard articulated by the Clinical Pharmacogenetics Implementation Consortium[1]. This paper examines the status of pharmacogenetics in various disciplines of medicine based on this evidentiary standard.
5. The result of a pharmacogenetic test must be integrated with other aspects of the patient's management. For this reason, pharmacogenetic testing should only be ordered as part of a clinical consultation and under medical supervision in an environment of informed consent and shared decision making with patients. Pharmacogenetics should not be provided as a "direct-to-consumer" service.
6. Most clinicians are unaware of the recent advances in pharmacogenetics and their impact on clinical practice. Educational resources and guidelines regarding the potential and limitations of pharmacogenetics should be developed for students and practising clinicians to address this lack of understanding.
7. The main source of funding for pharmacogenetic tests at present is the patient, without there being any recourse to a rebate from State or Federal Governments, or from insurers. **Medical** Colleges should make application for MBS-rebated funding of those pharmacogenetic tests which have a high level of evidence for validity and utility.

8. The implementation of pharmacogenetic testing has been compromised by inconsistencies in the naming of genes and variants, and in the interpretations provided by laboratories. The RCPA should ask the National Pathology Accreditation Advisory Council to review the requirements for pharmacogenetic testing to ensure that such testing complies with the usual standards for medical testing in Australia.
9. Research funding agencies and funders of healthcare in both the public and private sector should facilitate translational research on the implementation of pharmacogenetics in inpatient, outpatient, and community settings.

Introduction

Pharmacogenetics is the study of the interaction between a person's genes and the drug[1] they are taking. The term[2] is almost 60 years old[2,3], but it is only in the last 15 years that our ability to test and understand the function of these genes, together with the accumulating evidence of utility from clinical trials, have brought pharmacogenetics into clinical practice. Within the last 10 years, more than 21,000 articles on pharmacogenetics have been cited in PubMed, with the volume now growing at 200 articles per month. The clinical significance of pharmacogenetics is recognised by the FDA which includes pharmacogenetic information on ~15% of drug labels[4].

Pharmacogenetics is implicated in three aspects of a person's response to a drug:

- the genetic regulation of how the drug is handled within the patient
- the genetically-determined target of the drug in the patient
- the patient's genetic susceptibility to a severe adverse reaction to the drug.

These three aspects can be modified by inherited variations in one or more genes. For drugs directed against tumours, the genetically-determined target can also be modified by new mutations in a cancer i.e. by somatic "non-heritable" mutations. This document concentrates on the inherited genetic factors implicated in these three aspects; the clinical significance of somatic mutations in cancer as targets for selective chemotherapy lies outside the scope of this Statement.

Pharmacogenetics has the potential to both improve positive health outcomes and avoid negative outcomes. Clinical trials have now confirmed that pharmacogenetic testing achieves both goals[5–8], and can be cost-saving[9,10]. The avoidance of negative outcomes would, of itself, represent a significant saving for the Australian healthcare system: adverse drug reactions are implicated in approximately 3% of hospital admissions in Australia[11].

In a report commissioned by the Australian Centre for Health Research in 2008[12], the authors estimated that the Australian healthcare system would save over $1 billion per year by implementing pharmacogenetic testing and thereby avoiding many adverse drug reactions. Further substantial savings would accrue from avoiding wastage of drugs that were predicted to be ineffective for a patient, and from improved health outcomes for patients.

There is a comparative dearth of pharmacogenetics in clinical practice in Australia. In contrast to the FDA's inclusion of pharmacogenetic information on 15% of drug labels[4], there

[1] The term "drug" is used in this paper to refer to medication prescribed by a registered health practitioner for a medical purpose.

[2] The term "pharmacogenetics" refers to the analysis of one gene at a time, while "pharmacogenomics" refers to the analysis of multiple genes simultaneously. The latter term has eclipsed the former in recent years. Multi-gene analyses represent a greater challenge for laboratories to implement and interpret. However, for the prescribing clinician, the difference is immaterial as the key outcome is guidance for prescribing. The term "pharmacogenetics" is used throughout this document.

is no such requirement by Australian authorities. This deficiency is reflected in the lack of awareness of pharmacogenetics among local prescribers[13] and the lack of national guidelines regarding the use of pharmacogenetic tests.

This Position Statement has been developed by representatives from a number of medical Colleges. The objective of the document is to inform colleagues and those involved in the development of health policy about the current status and potential of pharmacogenetics in healthcare, and to promote further translational studies in our healthcare systems.

Scientific background

When a person ingests a chemical, there is a suite of genetically-controlled processes that influences the biological consequences. The genes responsible for those processes vary between individuals, and hence the impact of each chemical on a person can also vary.

These principles apply to the ingestion of any chemical, including toxins and drugs. The variation in the genes responsible for these steps probably reflects adaptive responses to different toxins in the environment. With the development of pharmaceutical therapies, the clinical significance of these variations has moved from understanding differences in responses to toxins to understanding differences in response to drugs.

In general terms, the variations in how a drug is handled within the body can include:

- absorption of the drug through the intestinal wall
- modification of the drug by the liver, yielding metabolites which may have reduced or enhanced biological effect
- transport of the drug and metabolites from the blood into specific organs and cells
- binding of the drug and metabolites to a biological target in the cell; this includes the potential binding of the drug and its metabolites to immune cells which trigger an adverse reaction
- active excretion of the drug and metabolites from the cell into the blood stream
- active excretion from blood into bile, faeces, or urine.

This complexity is made more manageable by differentiating between **pharmacokinetics** (variation in a drug's absorption, distribution, metabolism, and excretion) and **pharmacodynamics** (variation in the drug's biological effect at the point of action). There is also a category of **immune-mediated drug-gene interaction**. It has long been recognised that an immune response can be elicited by complex biological molecules during, say, an infection; an immune response can also be elicited by a simple synthetic drug such as allopurinol (which has only 14 atoms).

The significance of any particular gene or variant may also depend on variants in other genes or the presence of other drugs. For example,

- there may be two metabolic pathways for a certain drug; a gene variant which renders one pathway ineffective may be of little consequence if the other pathway remains active
- if a patient is taking two drugs which are metabolised by the same pathway, genetic variants may compromise the pathway's capacity and result in accumulation of metabolites
- a drug may increase or reduce the activity of a gene in the pathway, potentially causing a change in the metabolism of that drug or of another drug being taken by the patient.

Genetic variation in pharmacokinetics, pharmacodynamics, and immune response can manifest as

- unexpected low or high blood concentrations of a drug or active metabolite (with consequent effects on the patient) despite the patient being given the recommended dose
- unexpected lack of or excessive response to a drug despite the blood concentration being in the normal range
- severe acute immunological reaction (skin rash, hepatitis etc.) on exposure to a drug that is typically well-tolerated.

The primary goal of pharmacogenetics is the avoidance of these adverse outcomes by analysing genes which underlie variations in how drugs are handled by an individual. Genetic analysis has the advantage of using common methods for DNA analysis that are widely available, thereby facilitating patients' access to pharmacogenetic testing. This includes the incorporation of pharmacogenetics into the analysis and reporting of a patient's entire genetic code (whole genome sequencing)[14]. However, the complexities noted above can make it challenging to provide accurate predictions based on genetic analysis alone. The inclusion of analyses of multiple drug metabolites ("pharmaco-metabolomics")[15] and statistical modelling of pharmacokinetics ("Bayesian dosing")[16] is likely to prove to be more accurate. Patients with a congenital metabolic disorder e.g. G6PD deficiency, may also be at risk of disturbed drug metabolism.

More than 1,200 different chemicals have been approved as drugs by regulatory agencies in the US, Europe and Asia. To date, less than 20 genes have been implicated in causing clinically significant differences in the handling of some of these drugs. The biochemical pathways involved are diverse and their delineation is incomplete. Nonetheless, it is clear that there are classes of drugs which share the same pathways and can be predicted to have similar pharmacokinetics and pharmacodynamics. On the other hand, the potential for an immune-mediated drug-gene interaction is probably specific for each drug rather than being generalised to a class of drugs.

Several published reviews summarise the biological basis of pharmacogenetics and provide an overview of developments in the field in the last 15 years[4,17,18].

An evidentiary standard for guidelines

Prescribing guidelines must be pragmatic, responsible, and evidence-based. The standard which provides the foundation for such guidelines should recognize that the primary purpose of pharmacogenetics is to reduce the risk or wastage associated with using a drug for a particular patient rather than prove its efficacy in the population. As noted above, randomized clinical trials may be necessary to justify prescribing a particular drug, but a lower level of evidence may be sufficient for personalising the dose for a patient or the selection of a different drug that is approved for the same purpose.

Rather than develop a local evidentiary standard, Australasian guidelines should utilise the standard articulated by the Clinical Pharmacogenetics Implementation Consortium (CPIC), an international group within the Pharmacogenetics Research Network[1] .

The CPIC categorisation includes two stages[15]. The first ranks the evidence linking a genetic result to a predicted effect on drug handling as follows:

Level 1 the evidence includes consistent results from well-designed, well-conducted studies.

Level 2 the evidence is sufficient to determine the effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, by the inability to generalize to routine practice, or by the indirect nature of the evidence.

Level 3 the evidence is insufficient to assess the effects on health outcomes because of the limited number of studies, insufficient power of the studies, important flaws in their design or in the way they were conducted, gaps in the chain of evidence, or lack of information.

The second step ranks the strength of the clinical recommendation based on this evidence:

A strong recommendation for the statement

B moderate recommendation for the statement

C optional recommendation for the statement

Hence the highest ranking is “1A”, denoting a strong recommendation for clinical practice which is based on consistent evidence from well-designed studies.

A limitation of this evidentiary standard is that it is currently applied to the interpretation of one drug-gene combination at a time. In reality, the handling of a drug is affected by multiple genes, and laboratories are increasingly providing multi-gene panels to guide prescribing. Given that one laboratory’s panel and interpretive algorithm may differ from another’s, there is growing emphasis on clinical trials that document the impact of a laboratory’s panel on patient outcomes[5–8,20]. However, there are relatively few providers that have reported this type of evidence[21].

The application of the CPIC standard should not be used to extend pharmacogenetics beyond the intended scope. The evidence to justify a clinical interpretation of a pharmacogenetics test does not mean that the result should dictate the choice of drug or dose, or that testing should be done for every patient, or that appropriate clinical restrictions on prescribing can be ignored.

It is important to distinguish the evidentiary foundation of guidelines from the guidelines themselves. Prescribing practices, the availability of certain drugs, and the prevalence of pharmacogenetic variants differ across national and ethnic borders. For this reason, evidence-based guidelines for the use of a particular pharmacogenetic test may vary in different jurisdictions, despite those guidelines being grounded on the same evidentiary standard. This distinction is recognised by CPIC. In addition to providing an evidentiary standard, CPIC also provides guidelines regarding the clinical interpretation of pharmacogenetic variants that have been identified in a patient sample, but the guidelines stop short of advising which patients should have testing for such variants.

The acceptance of the CPIC evidentiary standard does not absolve Australian professional and regulatory bodies from the responsibility of developing appropriate guidance and standards for local clinicians and patients. Such guidelines may reference both pharmacogenetics and other strategies such as pharmaco-metabolomics and Bayesian dosing. The marketing, utilisation, and reporting of pharmacogenetic testing in Australia should be reviewed regularly to ensure that guidelines are sufficiently detailed and substantiated to be used with confidence[22].

The potential scale of pharmacogenetics in Australia

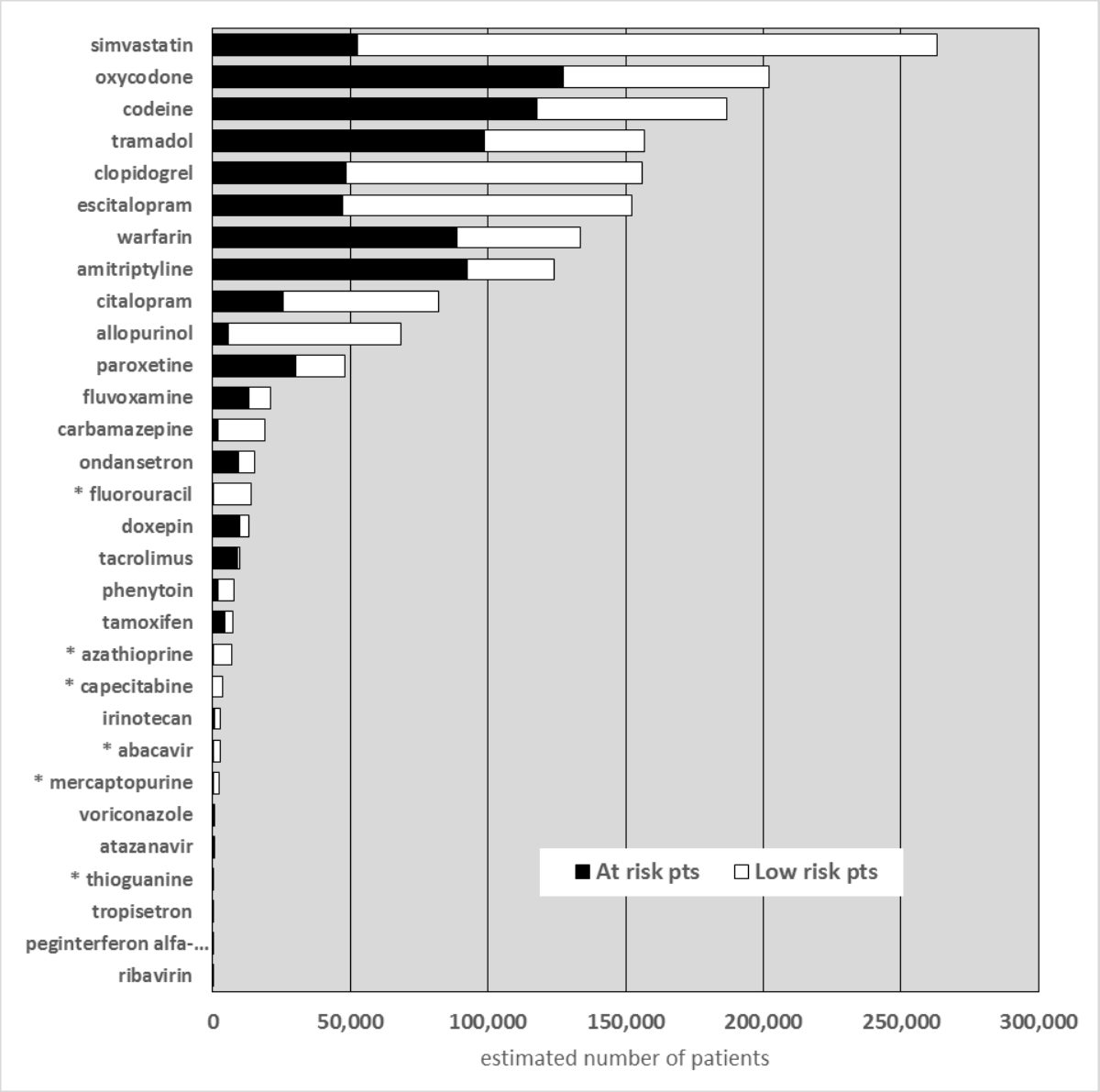
CPIC has identified 15 genes with a high level of evidence (1A) for guiding the prescribing of 30 different drugs. The genes identified by CPIC are, CYP2C9, CYP2C19, CYP2D6, CYP3A5, CYP4F2, DPYD, HLA-A*3101, HLA-B*5701, HLA-B*5801, HLA-B*1502, IFNL3, SLCO1B1, TPMT, UGT1A1, VKORC1.

Each gene is implicated in the metabolism of 1-10 drugs, and each drug is metabolised by 1-3 genes. The frequency with which the drugs are prescribed varies widely, as does the probability that a person has a “risk” variant in a given gene. Overall, approximately 1.7 million patients were dispensed these drugs in Australia in 2017, and approximately 40% of new patients being prescribed these drugs would be expected to have one or more “risk” variants in a pertinent gene[3].

The Figure below ranks the drugs selected by CPIC according to the estimated number of patients prescribed the drug in Australia during 2017. For each group of patients taking the drug, the proportion of new patients that would be likely to have a risk variant in one or more of the pertinent genes is shown.

All of the drug-gene combinations captured in this Figure carry a risk of lack of efficacy or of adverse reactions; drugs with an asterisk carry a risk of a lethal reaction to the drug. Of the six drugs which carry a risk of a lethal reaction, pharmacogenetic testing is available on the MBS for two genes covering four of the drugs. There is no MBS-rebate for any other pharmacogenetic testing.

[3] The CPIC list of drug-gene combinations having the highest level of evidence for clinical interpretation and action was reviewed in February 2018. The list of drugs was restricted to those on the PBS in 2017. The number of patients taking a drug was estimated as the number of prescriptions dispensed divided by 12 i.e. assuming one prescription per month. The frequency of “risk” variants in the pertinent genes was taken from CPIC data, with a preference for allele frequencies from Western European “general populations”. We need to emphasise the limitations of Western European populations in the Australian context.



The application of pharmacogenetics in Australia

The potential application of pharmacogenetics has been well-described in a recent review[4]. We provide some specific examples below, but emphasise that these discussions are neither exhaustive nor exclusive. Each of the drug-gene combinations discussed below is categorised by CPIC as having the highest level of evidence and strength of recommendation (Level 1A) for test-guided prescribing.

Psychiatry

The pharmacological management of depression is challenging, with only 50% of patients responding to their initial drug and there being a prolonged trial and error approach to drug selection and dose. Less than 50% of depressed patients achieve remission within 12 months of commencing therapy[23]. There are two genes, CYP2D6 and CYP2C19, which are primarily responsible for the metabolism of many psychotropic drugs. Approximately 1 in 6 people have variations in CYP2D6 that slow drug metabolism, while 1 in 3 have variants in CYP2C19 that accelerate drug metabolism[24]. Multiple clinical trials have now demonstrated that testing of these genes is relevant for prescribing[5,25–28]. The improvement in care arising from such testing has

also been documented; patients with very fast or very slow drug metabolism have 67% more medical visits and four-fold more disability claims than those with normal pharmacogenetic test results (unless prescribing is adapted to reflect their test results)[29].

Neurology

Carbamazepine is widely prescribed as an anticonvulsant, and also plays an important role in the management of pain and some psychiatric disorders. Among patients from China, India, and South East Asia, there is a common variant in the HLA gene complex (HLA-B*1502) which greatly increases the risk of life-threatening adverse skin reaction to the drug[30]. The Singaporean Government has recently mandated testing for HLA-B*1502 prior to prescribing carbamazepine[4]. The CPIC Guidelines note the negative predictive value of the test i.e. very low risk of an adverse reaction if the patients lacks HLA-B*1502, and the option of considering an alternate therapy in patients with HLA-B*1502[31]. For unknown reasons, this susceptibility is not evident among patients from other ethnic groups who have the same variant.

Cytotoxic therapy

Up to 5% of the population have a variant in the DPYD gene that slows metabolism of 5-flurouracil and capecitabine; both are widely used in cancer treatment. Patients with the DPYD variant are likely to develop serious manifestations of toxicity, and these can be life-threatening. Testing prior to commencement of therapy allows such patients to be commenced on half the usual dose[32,33]. It is important to note that, in this instance, patients can continue to take the drug; it is only the dose that is being managed.

There is a similar risk (and recommended management) for patients with a variant of the TPMT gene. Approximately 1:300 people have variants in the TPMT gene which slow the metabolism azathioprine, causing rapid accumulation and life-threatening toxicity. Azathioprine is widely prescribed in the management of cancer, chronic inflammation, and immune suppression. Pre-treatment testing for the TPMT gene variants, or of the corresponding enzyme activity, is widely used in such patients[34] and is one of only two pharmacogenetic tests listed on the MBS.

Breast cancer

Patients with hormone-sensitive breast cancer are frequently treated with tamoxifen. The CYP2D6 gene is responsible for converting tamoxifen to a more active metabolite. Variants in this gene are both common and associated with significant changes in tamoxifen pharmacokinetics. Clinical studies of the clinical utility of CYP2D6 testing in the management of breast cancer have been hampered by poor study design and flawed testing methods[35]. However, there is good evidence that testing (and subsequent adjustment of dose) is beneficial in women with post-menopausal breast cancer being treated with tamoxifen alone[36].

Rheumatology

Allopurinol is a first-line treatment for gout and hyperuricaemia. There is a variant in the HLA gene complex (HLA-B*5801) that places patients from various ethnic groups at relatively high risk of developing severe adverse skin reactions to the drug. The identification of at-risk patients prior to commencement of therapy reduces the

---

4 http://www.hsa.gov.sg/content/hsa/en/Health_Products_Regulation/Safety_Information_and_Product_Recalls/Product_Safety_Alerts/2016/hla-b-1502-genotypingandcarbamazepineinducedseverecutaneousadver.html

expected morbidity by either directing patients to alternative drugs[37] or introducing allopurinol with a tolerance-inducing protocol[38].

Pain management

Variants of the CYP2D6 gene result in much more rapid conversion of codeine to an active metabolite, morphine. Approximately 1% of Caucasians have such variants and are at increased risk of the adverse effects of morphine such as constipation, dizziness and respiratory depression[39]. These “rapid variants” are over-represented in studies of codeine-related deaths in children[40] and adults[41], and are associated with high levels of morphine in breast milk (with potentially fatal consequences for the infant)[42]. Notwithstanding the restriction being placed on over-the-counter purchase of codeine, such testing remains relevant for clinicians prescribing codeine[43].

Human Immunodeficiency Virus (HIV)

The anti-retroviral drug, abacavir, is widely used in the management of HIV. There is a variant in the HLA gene complex (HLA-B*5701) that places 5% of patients at high risk of developing severe adverse skin reactions to the drug. The identification of at-risk patients prior to commencement of therapy reduces the expected morbidity by directing patients to alternative drugs[44]. This test is one of only two pharmacogenetic tests listed on the MBS.

Challenges in implementation

There remain considerable challenges in defining the best way to use pharmacogenetic testing in specific clinical settings.

- For some disorders, the symptoms targeted by the drug and hence the clinical utility of pharmacogenetic testing, are hard to quantify. For example, pain is a subjective phenomenon that is modified by a wide variety of factors and managed with a wide range of strategies. This makes it challenging to provide quantitative evidence of the utility of pharmacogenetic testing.
- In some contexts, there are competing clinical factors that dwarf the potential impact of pharmacogenetics on prescribing decisions. For example, patients in intensive care typically have compromised function in multiple organ systems which, together with major interventions such as dialysis, will disturb the absorption, distribution, and metabolism of many drugs.
- There can be major differences in the frequency of gene variants in different ethnic groups[24], including in Aboriginal and Torres Strait Islander people[45]. This is particularly relevant in Australia’s increasingly diverse population. For this reason, therapeutic drug monitoring may still be required.
- As noted above, there are numerous multi-gene pharmacogenetic panels and associated interpretive algorithms for which no evidence of clinical utility has been published[21].

The integration of the patient’s history, clinical features, pharmacogenetic test result, other drugs, and therapeutic drug levels (if performed) has not been embedded in proven algorithms and hence remains a matter of clinical judgement. This variety and the potential significance of confounding factors dictates that pharmacogenetics not be used as the sole arbiter of prescribing decisions.

These challenges reinforce the need for Australian guidelines for the use of pharmacogenetics and related disciplines, and for these guidelines to be readily updated to reflect the rapid accumulation of knowledge.

Pre-emptive panel testing

Pharmacogenetic testing may be initiated in response to a particular clinical event e.g. poor response to therapy, or prior to the administration of a specific drug e.g. testing the TPMT gene before prescribing azathioprine[46].

Another strategy would be to test a panel of pharmacogenetic genes pre-emptively before a patient is prescribed any drug. Pre-emptive pharmacogenetic testing has the advantage of ensuring that potentially relevant information is immediately available at any time in the future. The potential of pre-emptive pharmacogenetics testing to improve the utility and cost-effectiveness of prescribing has been explored in a few structured clinical settings with encouraging outcomes[47–49]. Nonetheless, it remains a presumption that such testing is of benefit in terms of costs and healthcare outcomes overall [50] and further research is recommended[51].

Laboratory requirements

Samples for genetic testing

Pharmacogenetics involves the identification of specific pre-defined genetic variants, and does not necessarily require large amounts of high quality DNA. In clinical terms, this means that a buccal swab may be sufficient for pharmacogenetic testing. A fresh blood sample is preferred because the quality and quantity of DNA extracted from lymphocytes is superior to that obtained from buccal cells, but issues of convenience and patient preference may dictate the use of a buccal swab.

The most common time at which errors occur in medical testing is during pre-analytical processes, including sample collection[52]. Buccal swabs should be collected under the same conditions of sample control as is associated with a blood sample. Unsupervised collection of buccal swabs by patients or inexperienced staff raises the possibility that the swabs could have inadequate cellular material (compromising the quality of the analytical results) or be inadequately identified (leading to misapplication of the results to a different person).

Accuracy of the genetic result

There is a complex relationship between specific changes in the DNA sequence of a pharmacogenetic gene and the functional impact on the enzyme derived from that gene. Conventions have been developed (“star-allele” system) to simplify the naming of certain patterns of variations within a gene.

The identification of a single change in a gene sequence is not necessarily sufficient to provide unique identification of the overall pattern of variants in that gene[53]. Hence laboratory reports should clearly identify whether a gene’s star-allele has been unequivocally identified or whether it is simply the most likely consequence of an identified variation in DNA sequence.

The “star-allele” nomenclature has also been compromised by a lack of consistency in reference sequences and variant nomenclature, in both laboratory reports and the medical literature. International guidelines now mandate a more robust nomenclature for specifying variants identified in pharmacogenetic genes[53]. Laboratories may include the “star-allele” nomenclature as an alias, but it should not be a substitute for the formal approved nomenclature.

Clinical interpretation of the genetic result

Correct identification of the pharmacogenetic variants in the gene, and the predicted consequences for enzyme activity, do not necessarily provide useful information for the

prescribing practitioner[54]. It is essential that laboratory reports of pharmacogenetics testing provide specific, substantiated prescribing recommendations to guide the requesting clinician in the presentation of risk information and shared decision making with patients. The CPIC evidentiary standard, and the interpretation guidelines for specific drug-gene combinations developed by CPIC[1], provide a foundation for responsible reporting.

Ethics and privacy

Pharmacogenetic information should be managed with the same attention to ethics, consent and privacy as any other medical test; this includes informed financial consent (if applicable). However, the more detailed counselling considerations which apply to testing for heritable mutations in disease-causing genes, and the consequent considerations for relatives, do not necessarily apply. Most pharmacogenetic variants do not, of themselves, cause disease. Furthermore, a pharmacogenetic variant identified in a patient is only of relevance to a relative if two conditions are fulfilled: the relative is likely to be prescribed the same (or a related) drug and the variant identified is the principle determinant of the adverse outcome i.e. the susceptibility is inherited as an autosomal dominant trait. These conditions would rarely be met, and formal pre-test genetic counselling is not usually warranted. If the test methodology could potentially identify incidental findings i.e. for disorders unrelated to the primary purpose of testing, these possibilities would need to be formally addressed by pre-test genetic counselling.

The consent provided for a medical test is generally assumed to cover access by all health professionals involved in the care of a patient. This could potentially include access by any healthcare worker such as a pharmacist who is providing care for a different illnesses. In practical terms, pharmacogenetic information is likely to have low levels of sensitivity and may be suited to the broad consent procedures that are generally accepted by patients for medical investigations.

Notwithstanding the lack of novel ethical considerations regarding pharmacogenetics, any professional or agency handling personal health information must comply with the relevant laws and regulations. There are severe penalties for privacy breaches involving personal health data. Genetic information can be particularly problematic due to the uniqueness of each person's DNA data making it prone to re-identification. This is unlikely to be an issue if the genetic information is limited to the common variants typically identified by pharmacogenetic testing, but it would become relevant if the test methodology or clinical protocol e.g. in a clinical trial, yielded a much more detailed record of the patient's genetic code and clinical status[55].

Since July 2017, any Australian laboratory providing a test for medical purposes must be accredited to Australian Standards and have systems in place to ensure both the quality of testing and reporting, and the protection of data transmission and storage. This requirement extends to the provision of any test for medical purposes, and is not limited to testing that is rebated by Medicare.

Ordering pharmacogenetic tests

Pharmacogenetics should not be the sole basis for making a prescribing decision. Many factors should be considered before a prescribing decision can be made. For this reason, pharmacogenetic testing should be managed as a medical test requested by a healthcare professional with both the knowledge and accountability that is appropriate for the patient's care.

The regulations governing medical genetic laboratories in Australia[56] reinforce this principle, requiring that genetic testing only be provided in the context of a clinical consultation by a medical practitioner *viz.* "S1.1 The Laboratory must provide medical nucleic acid testing only in the context of a clinical service provided by a medical practitioner". This requirement protects the patient by ensuring that the whole context of testing is addressed by a clinician who is professionally and legally accountable. The requirement leaves open the possibility of a pharmacogenetic test being requested by a non-medical healthcare professional, but only in a team environment where a medical practitioner is accountable for the care provided to the individual patient.

This principle does not preclude the sharing of this information with other healthcare providers who are involved in the patient's care. Indeed, good care would require that important information be shared with the patient and with other healthcare professionals involved in the patient's care.

This principle precludes pharmacogenetics being marketed or implemented as a 'direct-to-consumer' offering.

Education

Surveys of medical practitioners in the US have demonstrated that over 95% of those surveyed agreed that genetic variation may influence drug response, but only 10-30%, felt adequately informed about testing[54,57]. The level of awareness and confidence is likely to be lower among other healthcare professionals.

This means that education in pharmacogenetics must address the principles underlying the discipline, the practicalities of testing, and the development of sufficient knowledge to use the result appropriately i.e. guidelines as well as protocols. This education must be delivered through an authoritative source in a way which minimises search time. It is not surprising that US physicians frequently rely on FDA-mandated drug labelling to inform their pharmacogenetic testing[58]. Conversely, it is striking that there is no such mandated guidance on Australian drugs[5].

There are numerous resources in pharmacogenetics now available to doctors, including

- **Web resources**. This relies on the ability of doctor to discern authoritative from non-authoritative information sources. Some web resources are authoritative but lack penetration. PharmGKB[6] is a respected international repository of curated information, but is not well known to the majority of healthcare practitioners and is challenging to navigate.
- **Clinical decision support tools**. These are generally considered authoritative e.g. UpToDate[7], with good penetration, although they cannot meet the clinician's need for local information such as the logistics of testing. When implemented well, decision support tools are highly effective in guiding good prescribing[59,60], and may be more effective than didactic presentations because they deliver knowledge at the point of care[61].
- **Educational materials** e.g. print, video, audio, meetings/conferences. Currently, these materials are often developed by test providers or professional societies. It may be useful to have a publicly accessible suite of short educational videos and associated materials provided by an authoritative source e.g. medical Colleges, that

[5] There is no PBS requirement for pre-treatment pharmacogenetic testing, even in the case of abacavir for which there is a specific MBS item. On the other hand, there are numerous targeted chemotherapeutic agents for which pre-treatment testing for somatic mutations is mandated.

[6] https://www.pharmgkb.org/index.jsp

[7] https://www.uptodate.com/

address different aspects of pharmacogenetic testing. Short videos could promote awareness and appropriate utilisation of pharmacogenetic testing by both patients and practitioners.

- **Undergraduate education**. Medical schools should incorporate pharmacogenetic teaching in their curricula.

Research

Studies of single drug-gene combinations have documented the analytical accuracy of pharmacogenetic tests, as well as confirming that the result is relevant for prescribing decisions. But a study of a single drug-gene combination does not necessarily reflect the reality of multiple genes being involved in the metabolism of a drug, and the clinical reality that patients are often taking multiple drugs. As a result, studies of single drug-gene combinations may struggle to document whether the test makes a significant difference to patient outcomes. On the other hand, studies of multiple drug-gene combinations are potentially too complex for detailed analysis of the pharmacokinetics of each permutation of drug and gene.

Rather than attempt detailed analysis of drug metabolites in the face of multiple gene variants, clinical trials are now randomising patients to those having pharmacogenetic testing (or not) and documenting patient outcomes[62]. Most trials have examined the use of a pharmacogenetic test to inform a specific prescribing decision e.g. the trials of pharmacogenetic testing for warfarin dosage[8]. These trials were mostly underpowered to detect effects on clinical outcomes such as bleeding or thrombosis and relied on surrogate measures of anticoagulation control[63]. Subsequent cost-effectiveness studies have applied the existing trial data and concluded that pharmacogenetic testing prior to warfarin prescribing could be cost-effective[64]. Governments will require this type of evidence to justify public funding of pharmacogenetic testing.

Nonetheless, exploring the value of pharmacogenetic testing to inform a single prescribing decision may not be the most appropriate perspective. A single test covering many common variants relevant to many potential prescribing decisions over time i.e. pre-emptive panel testing, is more likely to be cost-effective[65]. Assessment of this hypothesis will require clinical trials with measures of patient outcomes to document the clinical validity and cost-effectiveness[49]. Such studies must also address the challenges of implementing pharmacogenetic decision-support tools to ensure that clinicians have current advice in the future when a prescribing decision is made[64].

In Australia, over 117 million drugs are prescribed per annum in general practice[66]. The effectiveness of these drugs, the time taken to achieve this effectiveness, and the frequency of adverse drug reactions are potentially influenced by common pharmacogenetic variants, with major implications for the cost of healthcare. Thus far, trials of pre-emptive pharmacogenetic testing have usually been based on studies of inpatients and outpatients attending large medical centres in the USA[49]; European trials are underway. Pharmacogenetic trials in general practice are required to examine the impact of pre-emptive pharmacogenetic testing in the community. Such studies would also be crucial for informing GPs about this new area of practice, supporting the integration of pharmacogenetics in primary care, improving patient outcomes, and achieving cost savings.

Funding

Funding of diagnostic tests in Australia is provided through Medicare and State-funded programs or as an out-of-pocket expense for patients. Funding through Medicare requires Ministerial approval after a rigorous and lengthy approval process by the Medical Services

Advisory Committee (MSAC)[8]. As such, funding tends to lag behind technological advances. This is particularly relevant in genetic testing because each particular genetic test may require a separate approval process for each new indication.

There are only two pharmacogenetic tests currently listed on the Medical Benefits Schedule: tests of TPMT (item 73327) and HLA-B*5701 (items 71203 and 73323). There has not been an application for Medicare funding for another pharmacogenetic test[9], and so the lack of funding may reflect lack of assessment rather than rejection by MSAC. State funding tends to be focussed on acute inpatient care, and both State and Federal funding mechanisms have little capacity on legal or economic grounds to fund preventative health measures.

The RCPA conducted a survey of medical genetic testing that had been provided nationally in 2011[67] (currently being repeated for 2017). All of the testing of the CYP class of genes (the principle genes responsible for the majority of known drug-gene interactions) was paid for by patients, with no recourse to insurers or Medicare.

In the absence of Federal funding, pharmacogenetic testing will remain in the domain of clinical trials or as an out-of-pocket cost to patients. Hospitals in the public and private sectors may consider funding such testing as there is clear evidence that pharmacogenetics can be cost saving[68–71]. Given the financial benefit that would accrue to the Australian healthcare system from pharmacogenetic testing[12], it is likely that increased public funding will occur over time.

Conclusions

The purpose of this document is to draw the following conclusions to the attention of those providing healthcare and policy in Australasia:

- Pharmacogenetics is a well-established and growing discipline in developed healthcare systems overseas. The FDA includes pharmacogenetic guidance on 15% of medications[4] and pre-emptive pharmacogenetic is the focus of major studies in the US[49] and Europe[62].
- There is little evidence that these developments are being implemented in Australian healthcare. There is no pharmacogenetic guidance on PBS-listed medications, other than tests designed to limit the utilisation of certain chemotherapeutic drugs. There are very few clinical trials of pharmacogenetics in Australia at present[10].
- The lack of pharmacogenetic testing is potentially compromising the care of patients and adding a needless cost to the Australian healthcare system[12].
- The field is complex, the understanding of most clinicians is poor, and the implementation requires coordinated action across a number of domains. The introduction of pharmacogenetics needs to be managed to ensure that the right test is done for the right patient, and the right interpretation is provided to the clinician.
- The stakeholders who need to be engaged include
    - Patients
    - Funders, including Governments and health insurers
    - Medical schools and specialty Colleges
    - Pharmaceutical industry and pharmacists.

[8] http://www.msac.gov.au/

[9] As at May 2018, the MSAC website does not identify any applications referencing “CYP” genes.

[10] As at 4 December 2017, there was one trial on the Australian Clinical Trials register (https://www.australianclinicaltrials.gov.au/) that specified analysis of a pharmacogenetic gene; oncology trials were excluded.

This paper does not seek to provide a comprehensive list of the steps required to implement effective and responsible pharmacogenetic testing, and simply notes the following opportunities for progress in the short term:

Education

- The medical Colleges should develop a shared resource of extant pharmacogenetic educational tools for their trainees and Fellows.
- The medical Colleges should be surveyed to determine the teaching and assessment regarding pharmacogenetics in their postgraduate programs.

Guidelines

- Medical Colleges in Australia and New Zealand should develop context-specific guidelines for the use of pharmacogenetic testing.
- The Colleges should recommend that the NHMRC include pharmacogenetics in clinical practice guidelines (as appropriate), using the CPIC Guidelines as the evidentiary standard.
- The medical Colleges should approach the providers of patient management software regarding the provision of pharmacogenetic information at the point of care (or point of prescribing).

Funding

- The medical Colleges should submit applications for funding of tests of 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).

Quality

- The RCPA should review with the regulator (NPAAC and NATA/RCPA) the requirements for variant terminology and interpretation in pharmacogenetic reports, and whether a specific reference document should be developed by NPAAC to cover pharmacogenetic testing.

Research

- Providers of pharmacogenetic tests should be encouraged to implement clinical trials to determine the clinical utility of testing in general practice.

Acknowledgements

This document was developed under the auspices of the Royal College of Pathologists of Australasia. The College is grateful for the contributions of colleagues from other medical Colleges: Professor Jon Emery (RACGP), Dr Andrew Udy (CICM), Prof Andrew Somogyi (nominated by RACP), Prof Valsamma Eapen and Dr Vaidy Swaminathan (RANZCP), and Dr Chris Bain (ANZCA).

References

1. Caudle, K. E. *et al.* Incorporation of pharmacogenomics into routine clinical practice: the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline development process. *Curr. Drug Metab.* **15,** 209–17 (2014).

2. Motulsky, A. G. Drug reactions, enzymes, and biochemical geneticss. *JAMA* **165,** 835–7 (1957).

3. Evans, D. A. P. & Clarke, C. A. Pharmacogenetics. *Brit Med Bull* **17,** 234–240 (1961).

4. Relling, M. V & Evans, W. E. Pharmacogenomics in the clinic. *Nature* **526,** 343–350 (2015).

5. Elliott, L. S. *et al.* Clinical impact of pharmacogenetic profiling with a clinical decision support tool in polypharmacy home health patients: A prospective pilot randomized controlled trial. *PLoS One* **12,** e0170905 (2017).

6. Benitez, J., Jablonski, M. R., Allen, J. D. & Winner, J. G. The clinical validity and utility of

combinatorial pharmacogenomics: Enhancing patient outcomes. *Appl. Transl. genomics* **5,** 47–9 (2015).

7. Bousman, C. A. *et al.* Concordance between actual and pharmacogenetic predicted desvenlafaxine dose needed to achieve remission in major depressive disorder: A 10-week open-label study. *Pharmacogenet. Genomics* **27,** 1–6 (2016).

8. Wang, Z.-Q. *et al.* Pharmacogenetics-based warfarin dosing algorithm decreases time to stable anticoagulation and the risk of major hemorrhage: an updated meta-analysis of randomized controlled trials. *J. Cardiovasc. Pharmacol.* **65,** 364–370 (2015).

9. Berm, E. J. J. *et al.* Economic Evaluations of Pharmacogenetic and Pharmacogenomic Screening Tests: A Systematic Review. Second Update of the Literature. *PLoS One* **11,** e0146262 (2016).

10. Plumpton, C. O., Roberts, D., Pirmohamed, M. & Hughes, D. A. A Systematic Review of Economic Evaluations of Pharmacogenetic Testing for Prevention of Adverse Drug Reactions. *Pharmacoeconomics* **34,** 771–793 (2016).

11. Roughead, E. E., Semple, S. J. & Rosenfeld, E. The extent of medication errors and adverse drug reactions throughout the patient journey in acute care in Australia. *Int J Evid Based Heal.* **14,** 113–122 (2016).

12. *Improving the Quality Use of Medicines in Australia: Realising the potential of pharmacogenomics*. (2008).

13. Williamson, R. *et al. The Future of Precision Medicine in Australia. Report for the Australian Council of Learned Academies.* (2018).

14. Australian Health Ministers Advisory Council. *National Health Genomics Policy Framework*. (2017).

15. Neavin, D. *et al.* Pharmacometabolomics informs Pharmacogenomics. *Metabolomics* **12,** 1–10 (2016).

16. Donagher, J., Martin, J. H. & Barras, M. A. Individualised medicine: why we need Bayesian dosing. *Intern. Med. J.* **47,** 593–600 (2017).

17. Wang, L., McLeod, H. L. & Weinshilboum, R. M. Genomics and drug response. *N. Engl. J. Med.* **364,** 1144–53 (2011).

18. Weinshilboum, R. Inheritance and drug response. *N. Engl. J. Med.* **348,** 529–37 (2003).

19. Relling, M. V & Klein, T. E. CPIC : Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network. *Clin. Pharmacol. Ther.* **89,** 464–467 (2009).

20. Bradley, P. *et al.* Improved efficacy with targeted pharmacogenetic-guided treatment of patients with depression and anxiety: A randomized clinical trial demonstrating clinical utility. *J. Psychiatr. Res.* **96,** 100–107 (2018).

21. Bousman, C. A. & Hopwood, M. Commercial pharmacogenetic-based decision-support tools in psychiatry. *The Lancet Psychiatry* **366,** 1–6 (2016).

22. Somogyi, A. & Phillips, E. Genomic testing as a tool to optimise drug therapy. *Aust. Prescr.* **40,** 101–104 (2017).

23. Keks, N., Hope, J. & Keogh, S. Switching and stopping antidepressants. *Aust Prescr* **39,** 76–83 (2016).

24. Gaedigk, A., Sangkuhl, K., Whirl-Carrillo, M., Klein, T. & Leeder, J. S. Prediction of CYP2D6 phenotype from genotype across world populations. *Genet. Med.* **19,** 69–76 (2017).

25. Winner, J. G., Carbart, J.M., Altar, A., Allen, J.D., & Dechairo, B. M. A prospective randomized double blind study assessing the clinical impact of integrated pharmacogenomic testing for Major Depressive disorder. *Discov. Med.* **16,** 219–227 (2013).

26. Singh, A. B. Improved Antidepressant Remission in Major Depression via a Pharmacokinetic Pathway Polygene Pharmacogenetic Report. *Clin. Psychopharmacol. Neurosci. Neurosci.* **13,** 150–6 (2015).

27. Saldivar, J. S. *et al.* Initial assessment of the benefits of implementing pharmacogenetics into the medical management of patients in a long-term care facility. *Pharmgenomics Pers Med* **9,** 1–6 (2016).

28. Pérez, V. *et al.* Efficacy of prospective pharmacogenetic testing in the treatment of major depressive disorder: results of a randomized, double-blind clinical trial. *BMC Psychiatry* **17,** 250 (2017).

29. Winner, J., Allen, J. D., Altar, C. A. & Spahic-Mihajlovic, A. Psychiatric pharmacogenomics predicts health resource utilization of outpatients with anxiety and depression. *Transl. Psychiatry* **3,** e242 (2013).

30. Amstutz, U. *et al.* Recommendations for HLA-B15:02 and HLA-A31:01 genetic testing to reduce the risk of carbamazepine-induced hypersensitivity reactions. *Epilepsia* **55,** 496–506 (2014).

31. Caudle, K. *et al.* Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C9 and HLA-B Genotypes and Phenytoin Dosing. *Clinical Pharmacology and Therapeutics* **96,** 542–548 (2014).

32. Caudle, K. E. *et al.* Clinical Pharmacogenetics Implementation Consortium Guidelines for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing. *Clin. Pharmacol. Ther.* **94,** 640–645 (2013).

33. Lunenburg, C. A. T. C. *et al.* Prospective DPYD genotyping to reduce the risk of fluoropyrimidine-induced severe toxicity: Ready for prime time. *Eur. J. Cancer* **54,** 40–48 (2016).

34. Ford, L. T. & Berg, J. D. Thiopurine S-methyltransferase (TPMT) assessment prior to starting thiopurine drug treatment; a pharmacogenomic test whose time has come. *J. Clin. Pathol.* **63,** 288–95 (2010).

35. Province, M., Altman, R. & Klein, T. Interpreting the CYP2D6 Results From the International Tamoxifen Pharmacogenetics Consortium MA. *Clin. Pharmacol. Ther.* **29,** 997–1003 (2014).

36. Goetz, M. P. & Ingle, J. N. CYP2D6 genotype and tamoxifen: considerations for proper nonprospective studies. *Clin. Pharmacol. Ther.* **96,** 141–4 (2014).

37. Ko, T. M. *et al.* Use of HLA-B∗58:01 genotyping to prevent allopurinol induced severe cutaneous adverse reactions in Taiwan: National prospective cohort study. *BMJ* **351,** h4848 (2015).

38. Jung, J.-W. *et al.* An effective strategy to prevent allopurinol-induced hypersensitivity by HLA typing. *Genet. Med.* **17,** 807–814 (2015).

39. Gasche, Y. *et al.* Codeine intoxication associated with ultrarapid CYP2D6 metabolism. *N. Engl. J. Med.* **351,** 2827–2831 (2004).

40. Therapeutic Goods Administration (Australia). *Codeine use in children and ultra-rapid metabolisers*. (2015).

41. Lam, J. *et al.* Codeine-related deaths: The role of pharmacogenetics and drug interactions. *Forensic Sci. Int.* **239,** 50–56 (2014).

42. Koren, G., Cairns, J., Chitayat, D., Gaedigk, A. & Leeder, S. J. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. *Lancet (London, England)* **368,** 704 (2006).

43. Crews, K. R. *et al.* Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. *Clin. Pharmacol. Ther.* **95,** 376–82 (2014).

44. Mallal, S. *et al.* HLA-B*5701 screening for hypersensitivity to abacavir. *N. Engl. J. Med.* **358,** 568–79 (2008).

45. Griese, E. U. *et al.* Allele and genotype frequencies of polymorphic cytochromes P4502D6, 2C19 and 2E1 in aborigines from western Australia. *Pharmacogenetics* **11,** 69–76 (2001).

46. Somogyi, A., Coller, J. & Barratt, D. Pharmacogenetics of Opioid Response. *Clin. Pharmacol. Ther.* **97,** 125–127 (2015).

47. Van Driest, S. L. *et al.* Clinically actionable genotypes among 10,000 patients with preemptive pharmacogenomic testing. *Clin. Pharmacol. Ther.* **95,** 423–31 (2014).

48. Schildcrout, J. S. *et al.* Optimizing drug outcomes through pharmacogenetics: A case for preemptive genotyping. **92,** 235–242 (2013).

49. Dunnenberger, H. M. *et al.* Preemptive Clinical Pharmacogenetics Implementation: Current programs in five United States medical centers. *Annu Rev Pharmacol Toxicol* **55,** 89–106 (2015).

50. Janssens, A. C. J. W. & Deverka, P. A. Useless until proven effective: the clinical utility of preemptive pharmacogenetic testing. *Clin. Pharmacol. Ther.* **96,** 652–4 (2014).

51. Keeling, N. J. *et al.* Preemptive pharmacogenetic testing: exploring the knowledge and perspectives of US payers. **0,** 1–9 (2017).

52. Ravine, D. & Suthers, G. Quality standards and samples in genetic testing. *J. Clin. Pathol.* **65,** 389–393 (2012).

53. Kalman, L. V *et al.* Pharmacogenetic allele nomenclature: International workgroup recommendations for test result reporting. *Clin. Pharmacol. Ther.* **99,** 172–85 (2016).

54. Selkirk, C. G., Weissman, S. M., Anderson, A. & Hulick, P. J. Physicians' Preparedness for Integration of Genomic and Pharmacogenetic Testing into Practice Within a Major Healthcare System. *Genet. Test. Mol. Biomarkers* **17,** 219–225 (2013).

55. *National Statement on Ethical Conduct in Human Research 2007 (Updated March 2014).* (2014).

56. NPAAC. *Requirements for Medical Testing of Human Nucleic Acids (Second Edition)*. (2013).

57. Stanek, E. J. *et al.* Adoption of Pharmacogenomic Testing by US Physicians: Results of a Nationwide Survey. *Clin. Pharmacol. Ther.* **91,** 450–458 (2012).

58. Stanek, E., Sanders, C. & Frueh, F. Physician Awareness and Utilization of Food and Drug Administration (FDA)-Approved Labeling for Pharmacogenomic Testing Information. *J. Pers. Med.* **3,** 111–123 (2013).

59. O'Donnell, P. H. *et al.* Pharmacogenomics-Based Point-of-Care Clinical Decision Support Significantly Alters Drug Prescribing. *Clin. Pharmacol. Ther.* **102,** 859–869 (2017).

60. Kahan, N. R. *et al.* Large-scale, community-based trial of a personalized drug-related problem rectification system. *Am. J. Pharm. Benefits* **9,** 41–46 (2017).

61. Feero, W. G. & Green, E. D. Genomics education for health care professionals in the 21st century. *JAMA* **306,** 989–90 (2011).

62. Cecchin, E., Roncato, R., Guchelaar, H. j., Toffoli, G. & Ubiquitous Pharmacogenomics Consortium, for the. Ubiquitous Pharmacogenomics (U-PGx): The Time for Implementation is Now. An Horizon2020 Program to Drive Pharmacogenomics into Clinical Practice. *Curr. Pharm. Biotechnol.* **18,** 204–209 (2017).

63. Emery, J. D. Pharmacogenomic testing and warfarin: What evidence has the gift trial provided? *JAMA - Journal of the American Medical Association* **318,** 1110–1112 (2017).

64. Verhoef, T. I. *et al.* Cost-effectiveness of pharmacogenetic-guided dosing of warfarin in the United Kingdom and Sweden. *Pharmacogenomics J.* **16,** 478–484 (2016).

65. Brixner, D. *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. *J. Med. Econ.* **19,** 213–228 (2016).

66. Britt, H. *et al. General practice activity in Australia*. *General Practice Series* **40,** (Sydney University Press, 2014).

67. Mina, K. *Report of the RCPA Genetic Testing Survey 2011*. (2012).

68. Alagoz, O., Durham, D. & Kasirajan, K. Cost-effectiveness of one-time genetic testing to minimize lifetime adverse drug reactions. *Pharmacogenomics J.* 1–8 (2015). doi:10.1038/tpj.2015.39

69. Johnson, S. G., Gruntowicz, D., Chua, T. & Morlock, R. J. Financial Analysis of CYP2C19 Genotyping in Patients Receiving Dual Antiplatelet Therapy Following Acute Coronary Syndrome and Percutaneous Coronary Intervention. *J. Manag. Care Spec. Pharm.* **21,** 552–557 (2015).

70. Fagerness, J. *et al.* Pharmacogenetic-guided psychiatric intervention associated with increased adherence and cost savings. *Am. J. Manag. Care* **20,** e146-56 (2014).

71. Sultana, J., Cutroneo, P. & Trifirò, G. Clinical and economic burden of adverse drug reactions. *J. Pharmacol. Pharmacother.* **4,** S73–S77 (2013).