Pharmacogenomics in general practice

The time has come

CPD

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Background
Patients respond to medications differently because of variations in the genes that determine medication exposure and medication response.

Objective
The aim of this review is to introduce pharmacogenomic testing and explain how to start using pharmacogenomic tests in general practice.

Discussion
Knowledge of the variants in pharmacogenomics is useful when prescribing a variety of medications. International guidelines have identified at least 15 genes for which testing can inform the prescribing of 30 different medications with good evidence of clinical benefit. Nonetheless, pharmacogenomic tests should not be used as the sole basis for prescribing decisions, and should be considered in the context of other relevant clinical and laboratory features. General practitioners can incorporate pharmacogenomic tests into their clinical practice for patients with medication-related problems or those who are likely to require medications for which pharmacogenomics can provide guidance.

Clinical practice requires prescribing for one patient at a time

Randomised control trials (RCTs) are one of the most powerful tools for assessing the therapeutic effectiveness of medication to meet a clinical need.[1] These studies of patient populations provide the necessary evidence of efficacy for funding, regulatory applications and marketing. However, one of the limitations of RCTs for prescribing is that they describe the average effects of a medication in groups of patients rather than outcomes for individual patients. Every practising clinician has patients who fulfil the relevant clinical criteria for pharmacotherapy yet do not respond to the medication as expected based on the available evidence. A patient may not benefit from the medication at the highest recommended dose, they may show toxicity at a standard dose, or they may develop severe idiosyncratic adverse effects.

The challenge of prescribing antidepressants is just one example where the effectiveness shown in RCTs does not always translate into benefits for individual patients. Despite ensuring the correct diagnosis, adequate dose and medication adherence, up to two-thirds of patients with major depression fail to respond to the initial antidepressant.[2] The time taken to document a lack of response, and then manage a safe transition to another medication, constitutes an enormous burden on patients, families, their doctors and the funding of healthcare.

Pharmacogenomics and individualised prescribing

There is a relatively small number of genes for which there is a high level of evidence that genetic analysis should inform individualised prescribing. Many of these genes regulate the absorption, distribution, metabolism and excretion (ADME) of medications. The ADME processes determine what level of 'exposure' a patient will have to a medication. The speed of biochemical pathways involved in the metabolism of medications – for example, by the cytochrome P450 (CYP) class of enzymes – differs between individuals, resulting in an up to 100-fold variation in exposure to medications. This often explains why patients can respond differently to the same medication at the same dose.[3] Genetic differences in the ADME genes presumably reflect evolutionary responses to different environmental toxins in the distant past. Testing a patient for gene variants that cause extremes of medication exposure (too high or too low) can provide

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insight into why a patient is responding to a medication in a certain way, or perhaps not responding at all.

There is another group of genes that are not involved in ADME but influence medication responses directly. Some of these genes are predictive of severe and potentially life-threatening immune-mediated toxicities. Knowledge of whether a patient is susceptible to such reactions means that particular medications can be avoided; for example, carbamazepine should not be prescribed to patients with certain human leucocyte antigen (HLA) genotypes because of an increased risk of Stevens-Johnson syndrome and toxic epidermal necrolysis.[4] The potential for immune-mediated toxicities is probably specific for each medication rather than being generalised to a class of medications.

Knowledge of the gene variants influencing exposure or response (ie pharmacogenomics) allows prescribers to move from the general to the particular, and provide a scientific basis for individualised prescribing. The goal is more effective and safer choices of medication and dose (refer to Case studies).

The evidence for pharmacogenomics

Some commentators have criticised the evidence base for pharmacogenomics as being insufficient to justify the purpose for which it is promoted.[5,6] As a comparatively new field, there is certainly much work to be done in documenting the clinical utility of pharmacogenomics. That said, pharmacogenomics is typically used to choose between prescribing options that are *a priori* equivalent, and the threshold of evidence need not be as high as would be required to introduce into clinical practice a new medication with an uncertain risk–benefit profile. There is already a large body of peer-reviewed clinical evidence that has been collated and developed into prescribing guidelines by international expert bodies.[7] The utility of testing will also be dictated by the clinical context; for example, testing prior to prescribing for a specific purpose versus testing to inform unspecified prescribing in the future.

In support of the clinical implementation of pharmacogenomics, numerous trials have documented improvements in the probability and speed of remission when prescribing is guided by pharmacogenomic tests.[8–13] A report in 2008 estimated that the widespread implementation of such testing in Australia could yield savings in excess of $1 billion annually by the avoidance of adverse medication reactions alone.[14] Similar considerations have led the Food and Drug Administration (FDA) in the US to list pharmacogenomic information on 15% of medication labels.[3] Major trials of pre-emptive pharmacogenomic testing (ie prior to any prescription being considered) are underway in the US and Europe.[15–18] These large studies are powered to determine the extent of clinical and health economic benefits.

An important challenge in pharmacogenomics has been the lack of consistency in how laboratories report variations in different genes.[19] This challenge was met by the Clinical Pharmacogenetics Implementation Consortium (CPIC)[20] and the Dutch Pharmacogenetics Working Group (DPWG)[21], which both provide frameworks for evaluating medication–gene associations and expert guidance about prescribing for patients with given variants. There are some subtle differences between CPIC and DPWG based on differences in expert opinion, but there is concordance in the majority of cases. For example, the CPIC has identified 15 genes involved in the exposure or response to 30 medications for which the clinical utility of testing has the highest level of evidence (Table 1); the DPWG has developed a similar catalogue of clinically relevant medication–gene interactions.[21] The frequencies with which these medications are prescribed varies widely. There are also major differences in the frequencies of gene variants between ethnic groups,[22,23] resulting in differences in the probability of significant medication–gene interactions.

In February 2018, we reviewed the CPIC list of medication–gene combinations that have the highest level of evidence for clinical interpretation and action; the list of medications was restricted to those on the Pharmaceutical Benefits Scheme (PBS) in 2017. The number of prescriptions dispensed in Australia during 2017 was determined from the PBS website (http://medicarestatistics.humanservices.gov.au/statistics/pbs_item.jsp), and the number of patients taking a medication was estimated as the number of prescriptions dispensed divided by 12, 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'. Overall, approximately 1.7 million Australian patients were dispensed the medications identified by CPIC in 2017 (Table 1), and approximately 40% of new patients being prescribed these medications are predicted to have one or more 'risk' gene variants relevant for the medication prescribed. A recent study of 5400 Australians who underwent testing of just four ADME genes showed that 96% had at least one clinically actionable pharmacogenomic variant.[24] There are also hundreds of other medication–gene combinations for which evidence of clinical utility with pharmacogenomic testing is being accumulated and evaluated (visit the PharmGKP website for more information at www.pharmgkb.org).[7]

Limits to pharmacogenomics

There are some situations in which the pharmacogenomic test alone identifies a critical threat to the patient's health when exposed to a certain medication (eg avoidance of abacavir in patients with *HLA-B*5701*). More commonly, pharmacogenomics should not be used as the sole basis for prescribing decisions. Prescribing is a multifaceted, complex process which, to be done well, requires years of clinical experience. Pharmacogenomic information should be considered together with relevant clinical information, such as age, renal and liver functions; medication history; concurrent medications and level of patient understanding,[25] prior to prescribing. The availability of pharmacogenomic testing and authoritative guidelines does

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Table 1. Medication and gene combinations for which the Clinical Pharmacogenomic Implementation Consortium has assigned the highest level of evidence for clinical benefits.*

Medication	Estimated prevalence of pharmacogenomic susceptibility	Genes involved in medication exposure
Abacavir	7%	*HLA-B*5701*
Allopurinol	8%	*HLA-B*5801*
Amitriptyline	74%	*CYP2C19, CYP2D6*
Atazanavir	31%	*UGT1A1*
Azathioprine	4%	*TPMT*
Capecitabine	2%	*DPYD*
Carbamazepine	10%	*HLA-A3101, HLA-B1502*
Citalopram	31%	*CYP2C19*
Clopidogrel	31%	*CYP2C19*
Codeine	63%	*CYP2D6*
Doxepin	74%	*CYP2C19, CYP2D6*
Escitalopram	31%	*CYP2C19*
Fluorouracil	2%	*DPYD*
Fluvoxamine	63%	*CYP2D6*
Irinotecan	31%	*UGT1A1*
Mercaptopurine	4%	*TPMT*
Ondansetron	63%	*CYP2D6*
Oxycodone	63%	*CYP2D6*
Paroxetine	63%	*CYP2D6*
Peginterferon	40%	*IFNL3*
Phenytoin	26%	*CYP2C9, HLA-B1502*
Ribavirin	40%	*IFNL3*
Simvastatin	20%	*SLCO1B1*
Tacrolimus	92%	*CYP3A5*
Tamoxifen	63%	*CYP2D6*
Thioguanine	4%	*TPMT*
Tramadol	63%	*CYP2D6*
Tropisetron	63%	*CYP2D6*
Voriconazole	31%	*CYP2C19*
Warfarin	66%	*CYP2C9, CYP4F2, VKORC1*

**Medications not listed on the Pharmaceutical Benefits Scheme in 2017 are excluded.*

not dictate that every patient should be tested, that a specific drug or dose must be prescribed, that appropriate clinical restrictions on prescribing can be ignored, or that therapeutic drug monitoring is irrelevant.[26] Pharmacogenomic tests should be regarded as medical tests requested by a healthcare professional with the knowledge and accountability appropriate for the patient's care.

Implementing pharmacogenomics in general practice

Pharmacogenomic tests are now available through a number of providers in Australia. However, most general practitioners (GPs) are not trained to understand how pharmacogenomic test results are generated or how the underlying biology drives pharmacokinetics and prescribing guidance. However, this should not preclude the clinical use of pharmacogenomics on the basis of internationally agreed guidelines. We outline three major considerations for the responsible use of pharmacogenomics, and provide four case studies from general practice to illustrate the clinical utility.

As GPs are often required to initiate medications, the pharmacogenomics report should be 'user friendly' and include explicit, relevant prescribing advice. The analytical result of a pharmacogenomic test (ie the gene variants identified and the predicted changes in drug exposure and/or response) is not sufficient information for most busy GPs. A useful pharmacogenomics service provides an interpretation detailing the prescribing consequences arising from a result given the unique clinical scenario. This extra level of consultant support for GPs may or may not be required depending on their knowledge of and experience with pharmacogenomic testing.

As an initial step in using pharmacogenomics, it may be helpful for doctors to gain experience in testing patients with extant medication-related problems. An example of this may be a patient with treatment-resistant depression who has tried several antidepressants that were all ineffective, but referral pathways to specialised mental

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health services are unavailable or too slow. As confidence with pharmacogenomic testing grows, tests can be considered for patients who are likely to need particular medications in the future; such tests would include pre-emptive testing, which provides pharmacogenomic information that can be considered prior to prescribing any new medications.

GPs requesting pharmacogenomic testing should be critical users. Pharmacogenomics does not replace clinical assessment, other pathology or therapeutic drug monitoring. Pharmacogenomics informs, but does not replace, clinical judgement. Clinical judgement may include judging the quality and clinical applicability of direct-to-consumer testing conducted in Australia or overseas (case study 4).

Pharmacogenomics in Australia

Most doctors recognise the value of genetic testing of cancer to predict whether patients are eligible for specific, targeted pharmacotherapy.[27] Apart from these tests, there are only two items on the Medicare Benefits Schedule that inform individualised prescribing: a test for abacavir hypersensitivity (item 73323) and a test to guide dosing with thiopurines (item 73327).[19] In contrast to the FDA's position, the PBS listings for the medications in Table 1 make no mention of the potential benefit of pre-emptive genetic testing. The clinical utility of pharmacogenomics is not widely appreciated in Australia.

Pharmacogenomic testing by Australian laboratories is typically funded by patients. This is costly and prohibitive for some patients, although costs are decreasing all the time (a panel of common CYP enzymes costs $150–200). The disconnect between the evidence supporting pharmacogenomics and the availability of rebated testing is recognised in a recent position statement on pharmacogenomics developed by representatives from a number of major medical colleges and released by the Royal College of Pathologists of Australasia (www.rcpa.edu.au/Library/College-Policies/Position-Statements/Utilisation-of-pharmacogenetics-in-healthcare). Broader application of pharmacogenomics in general practice will occur when rebated tests become more widely available.

Conclusion

There is good evidence that pharmacogenomic testing can inform the prescribing of many medications used by GPs in Australia. These tests can be successfully incorporated into general practice by using a service that provides explicit prescribing advice with test results, gaining experience with patients who have medication-related problems and considering test results in the context of the overall clinical picture when making prescribing decisions.

It would be helpful to have better reimbursement for pharmacogenomics, more research in Australia, local education programs, Australian guidelines, and reports embedded in practice software and electronic health records. Nonetheless, while these issues are being addressed, responsible doctors can use the tests and evidence that are already available to improve prescribing decisions for their patients.

Case studies

CASE STUDY 1

A GP was caring for a woman aged 55 years with a history of anxiety and depression and no other medical problems. The patient was managed by a psychologist for many years. After the patient lost her job, her mood deteriorated, she spent most days in bed, and motivation for finding new work was poor. The decision was made to commence medication. Sertraline was started and titrated to 200 mg daily, the highest recommended dose. Several months of treatment failed to help, and sertraline was then swapped for citalopram. The patient deteriorated further on citalopram, and she required a psychiatric admission approximately six months after her initial clinical decline. Just prior to hospitalisation, the GP ordered pharmacogenomic tests. The results showed that she had low exposure to sertraline and citalopram due to high *CYP2C19* activity (*CYP2C19*17/*17*), leading to rapid metabolism of these antidepressants.[28] This information was forwarded to the treating psychiatry team. Venlafaxine was chosen as an alternative antidepressant because exposure is not as dependent on *CYP2C19*, and the patient recovered and came off medication 12 months later.

CASE STUDY 2

A man of Chinese ethnicity aged 67 years presented with gout and hyperuricaemia. While considering the best course of management, his GP recalled that approximately 1 in 300 such patients will develop a severe drug rash with eosinophilia on exposure to allopurinol. Allopurinol is effective in the treatment of hyperuricaemia, and the risk of this severe cutaneous adverse reaction (SCAR) is low. Nonetheless, SCAR is a dangerous phenomenon with documented mortality rates of up to 35%.[29] Among Han Chinese, this hypersensitivity to allopurinol is closely linked to a specific *HLA-B* allele, **5801*, which is found in 20% of the population. Testing performed prior to commencement of treatment documented that this patient did not have the **5801* allele, and hence was at very low risk of developing SCAR with allopurinol.

CASE STUDY 3

A woman aged 71 years with atrial fibrillation and other chronic comorbidities was on and off warfarin multiple times during many hospital admissions over a two-year period. When taking warfarin, the international normalised ratio (INR) was very sensitive and unstable, with doses between 0.5 mg and 1 mg daily putting the INR within therapeutic range for less than half the time. Her extreme sensitivity to warfarin had practical implications. Because 1 mg tablets are the smallest available, titrating doses by splitting tablets is inaccurate. This dilemma commenced a merry-go-round of warfarin or a direct

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oral anticoagulant (DOAC) dependent on the prescribing doctor. Pharmacogenomic testing by the GP showed the woman to be a normal metaboliser of warfarin (*CYP2C9*1/*1*) but highly sensitivity to warfarin at the vitamin K cycle (*VKORC1*).[30] This information helped with the decision to cease warfarin for the final time and use a DOAC for stroke prevention, a decision that was communicated prospectively to her treating teams.

CASE STUDY 4

A fit man visited his GP after turning 50 years of age for his first health check in years. He brought to the appointment the results of pharmacogenomic tests performed via the local pharmacy. The tests were taken because his parents both had heart attacks and his wife thought the tests could predict 'heart trouble'. The health check results were normal except for a total cholesterol of 7.8 mmol/L. The decision was made to start a statin. Because the GP remembered seeing something about statins in the pharmacogenomic report, the report was considered in more detail at the follow-up appointment. The patient had low activity of the main transporter responsible for taking simvastatin and atorvastatin into the liver (*SLCO1B1*5/*17*), a result associated with higher exposure to simvastatin and higher rates of statin-associated muscle toxicity compared with other genetic variants.[31] Rosuvastatin exposure is less pronounced in patients with this genotype, and so it was chosen rather than simvastatin or atorvastatin.

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