November 2019 Edition no. 63

AMPATHCHAT

Dr Jessica Trusler, Dr David Haarburger, Dr Carolyn Fedler

PHARMACOGENOMICS: A guide to a new laboratory test to predict drug responses and improve drug adherence and patient outcomes

Background

It is well established that unique patient characteristics exist to guide therapeutic drug decision making. These assist in optimising drug response and minimising adverse drug reactions (ADRs), and include age, weight, diet, co-morbidities, liver and renal function, as well as drug-drug interactions.

The concept of genetic variation, which affects drug response, dates back to the 1940s. In 1959, the term "pharmacogenetics" was coined to describe inherited genetic variations in a single gene, which influences drug response. After decades of research, evidence is considered sufficient to warrant the application of pharmacogenetics to routine clinical practice. Using advanced molecular technologies, many genes coding for enzymes involved in drug metabolism (e.g. cytochrome enzymes) can now be tested for simultaneously on a single platform. Thus was born the concept of pharmacogenomics, studying the effect of multiple gene variabilities on drug metabolism and its direct integration into patient care.

One of the earliest and best-known examples of this is the screening of patients for variations of the thiopurine methyltransferase (TPMT) gene, which is used to guide thiopurine dosing used in chemotherapy and immunosuppression:

- Three in 1 000 people have no working copy of the TPMT gene.
- Some 10% of people have a gene variant that is less active than the rest of the population, and in these individuals, a standard course of treatment can result in them suffering from severe ADRs, leading to possible hospitalisation.

Patients with absent TPMT activity should not receive thiopurine drugs, and those with reduced TPMT activity should be monitored and treated under specialist supervision. The current recommendations are that doctors should consider measuring TPMT activity before starting therapy with azathioprine, mercaptopurine or thioguanine. An easier way is to analyse the single-gene TPMT. This is currently a separate routine test offered by Ampath.

Throughout the 21st century, clinical use of other single-gene drug pairs to guide drug choice and dosage has increased. Examples include CYP2C19-clopidogrel, CYP2C9/VKORC1-warfarin, CYP2D6-opioids, CYP2D6-tamoxifen, DPYD-fluoropyrimidines, HLA-B*15:02-carbamazepine and HLA-B*57:01-abacavir.

Why is pharmacogenomics important in your practice and what are the benefits to your patients?

Ampath's new pharmacogenomics panel will guide recommendations regarding the prescription of over 140 drugs from several clinical categories: **cancer, cardiovascular, diabetes, gastrointestinal, gynaecology, haematology, infectious disease, neurology, pain, psychiatry, rheumatology, transplantation and urology.**

- Drug interventions are effective in only 30 to 60% of patients.
- Some 1 500 000 ADRs are reported annually worldwide.
- ADRs are an important cause of hospital admissions, accounting for 6.5% of all hospitalisations in two large hospitals in the UK. Recent surveys have shown that ADRs were the fourth leading cause of in-hospital mortality in all hospitals in the USA.
- Worldwide, annual costs associated with ADRs amount to $136 billion.
- Non-compliance: one in three people stop taking prescribed medication due to negative side effects.

Where else have these tests been shown to be useful?

A recent large study was performed by Coriell and ThermoFisher, which analysed pharmacogenomics on over 5 000 retired teachers in Kentucky, USA. These people were taking an average of 12 different medications each. After testing, it was discovered that 64% of these people required an immediate medication change.

Benefits to the patient one year after medications were changed following pharmacogenetic testing

- A 29% decrease in hospitalisation
- An 18% decrease in pharmacy spend
- A 24% decrease in slips and falls

Indirect benefits

- A 17% decrease in cost to healthcare plan spending after six months
- A 94% physician adherence to pharmacist review
- A 19.5% overall decrease in healthcare plan costs

How does pharmacogenomics work?

Genetic variability is a complex topic. As outlined above, mutations occur within genes that code for enzymes that are responsible for pathways in the drug transport and metabolism process. Figure 1 provides a simplified

representation of how gene mutations may result in a change in the function of a critical metabolising enzyme, and its resulting effect on the metabolism of the administered drug.

Fast or slow metaboliser? Deciding the drug dosage

Variation in genes affect how slowly or quickly a drug is metabolised in the body. The effect of this depends on whether the administered drug is pharmacologically active or a prodrug that needs to be metabolised into its active form.

By identifying and classifying genetic variations within populations, four classes of drug therapy responses have been identified:

- **Absent or poor metabolisers:** Consider alternative therapy due to likely side effects or reduced or no production of the active drug metabolite
- **Intermediate metabolisers:** The drug is not completely effective; use with caution, adjust dose, and ensure monitoring or supervision
- **Normal metabolisers:** The drug is considered to be effective and safe in these people; use with standard precautions
- **Extensive/ultra-rapid metabolisers:** The drug may be contraindicated due to a reduced clinical effect, toxicity or excessive effect; consider alternative therapy

Pharmacogenomics testing at Ampath

This is an extensive pharmacogenomics test, which includes 13 genes that are important in both drug metabolism (nine genes) and risk prediction (four genes). The following drug metabolising genes are included: COMT, CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, SLCO1B1 and VKORC1. The following risk prediction genes are included: Apolipoprotein E (ApoE), Factor II, Factor V Leiden and methylenetetrahydrofolate reductase (MTHFR).

Pharmacogenomics test collection and report access information

- Sample collection requirements: One full tube of EDTA blood at any Ampath depot nationally.
- The test is run in the Genetics Department of Ampath's National Reference Laboratory (NRL).
- Turnaround time: 10 days for the electronic report to be available.
- The test price is R1950 in 2019, and effective from 1 January 2020, is R2044 inclusive of 15% VAT.

Due to the size of the report, access to the report is electronic and is compliant with the Protection of Personal Information Act. Only the referring doctor, copy doctor and patient will have access to the report. The summary report consists of five to six pages, divided into drug and clinical categories. The report provides usage information for each drug, and groups the drugs into the following categories:

1. **Use with standard precautions:** The medication is expected to be effective at standard drug doses for the patient
2. **Use with caution:** The recommended dose of medication may need to be adjusted for the patient, and/or vigilance increased for adverse effects
3. **Consider alternatives:** Medication potentially has reduced efficacy or increased toxicity; an alternative medication is typically recommended

The patient may retain the last page of the report to share it with other clinicians and pharmacists as a pharmacogenomic gene summary. In addition to the summary Ampath report, if required, the patient or clinician may download a detailed comprehensive report of more than 55 pages from a unique URL link that appears at the end of each report. All providers are required to register for email reports in order to gain access to the report in a suitable format. Patients can register on the Ampath patient results portal to access their results.

Summary benefits of Ampath's pharmacogenomic testing:

A single test can now be applied to assist in predicting risk when prescribing a large number of drugs used in everyday clinical practice. This may assist in avoiding side-effects, ADRs and could mitigate medico-legal risks.

The turnaround time for the results is under 10 days, and the test only needs to be performed once.

References available upon request.

Figure 1: