AMPATHCHAT no. 84

IMPROVING PATIENT CARE WITH PHARMACOGENOMIC TESTING

Dr Janin Alant and Karmishtha Hutheram

KEY MESSAGES

- Pharmacogenomic testing (PGT) investigates the way an individual's genetic make-up influences their response to various types of medication.
- Pre-emptive PGT can reduce adverse drug reactions and improve patient compliance.
- PGT is increasingly being performed through larger panel-based testing like the PGx120, making it more cost-effective and accessible.
- Results of PGT should always be interpreted in conjunction with the observed clinical response while also considering other non-genetic factors that may affect drug metabolism and efficacy.

Sample type	Buccal swab or peripheral blood sample (EDTA)
Mnemonic	PHARMA
Turnaround time	10 working days from sample being received at the NRL Genetics Laboratory

INTRODUCTION

Ampath is proud to be a leading provider of pharmacogenomic testing (PGT) in South Africa. PGT investigates the way an individual's genetic make-up influences their response to various types of medication. Small genetic changes within known pharmacogenes (such as the cytochrome P450 system) affect how well the relevant P450 enzyme functions with regard to the absorption, distribution, metabolism or excretion of target medications. Harnessing this information allows for personalised prescribing and dosing, ultimately leading to improved outcomes and reduced adverse drug reactions.

Evidence supporting the clinical benefit of PGT has been growing steadily. Internationally, several professional bodies are now advocating for the implementation of PGT into primary care services. One of the largest published multicentre studies to date demonstrated a 30% reduction in clinically relevant adverse drug reactions using pre-emptive PGT within diverse healthcare settings across seven European countries. The American Food and Drug Administration (FDA) has already incorporated PGT-directed dosing guidelines into the package inserts of more than 299 medications (as of 31 December 2020). Locally, the South African Health Products Regulatory Authority (SAPHRA) recently added *CYP2C9* genotyping as a requirement prior to Siponimod administration, and such further examples are expected to follow, as more South African population-specific genotyping data emerges.

HOW IS PHARMACOGENOMIC EVIDENCE REVIEWED AND CURATED?

Pharmacogenetics is a very active field of research with significant amounts of peer-reviewed data being published every year. Translating this growing body of evidence into clinical practice has, however, been a slow process. The Clinical Pharmacogenomics Implementation Consortium (CPIC) was established in 2011 to drive and facilitate the clinical implementation of PGT across medical disciplines. The CPIC website is an open-access resource that regularly publishes updated and peer-reviewed guidelines on specific drug-gene interactions and their resultant dosing adjustments or recommendations. The evidence available in support of specific recommendations or associations is stringently graded in terms of both strength and quality (assigned as levels A to D) and updated regularly as new evidence emerges. Other highly-regarded and commonly-used PGT resources include the Pharmacogenomics Knowledge Base (PharmGKB) and the Dutch Pharmacogenetics Working Group (DPWG).

HOW IS PHARMACOGENOMIC TESTING TYPICALLY PERFORMED?

Pharmacogenomic testing can be performed as a targeted single gene test (e.g. *TPMT* genotyping prior to thiopurine administration) or through larger panel-based testing, which collectively assesses for numerous drug or gene combinations in one assay. Panels often differ in terms of the number of genes covered and the number of genetic changes or single nucleotide polymorphisms (SNPs) that are detectable within each gene. The accessibility and cost-efficiency of panel-based PGT has improved significantly in recent years. The PGX120 panel (PHARMA), which is now offered at Ampath Laboratories, detects ~120 different genetic changes across 36 known pharmacogenes with genotype-based dosing algorithms provided for over 150 medications.

IMPLEMENTING PHARMACOGENOMIC TESTING IN ROUTINE CLINICAL PRACTICE

There are now numerous examples of how PGT can affect and improve prescribing practices and reduce adverse drug reactions. A few key examples of the utility of PGT in general practice are discussed and highlighted below.

Codeine

Codeine is one of the most commonly prescribed analgesics in both adult and paediatric patients, and forms part of numerous over-the-counter products in South Africa. Codeine is administered as a pro-drug, which is converted to morphine through the action of the CYP2D6 enzyme. Genetic changes within the *CYP2D6* gene affect how well this conversion to morphine occurs. Individuals who carry additional copies of the *CYP2D6* gene are known as ultra-rapid metabolisers. They have a significantly increased risk of toxicity after codeine or tramadol administration.

Reports of severe respiratory depression and death in children who were ultra-rapid metabolisers and who received codeine post-tonsillectomy are well documented and have prompted an FDA black box warning highlighting this risk. Poor metabolisers, on the other hand, will have a poor therapeutic response to codeine. Pre-emptive PGT can identify these ultra-rapid and poor metabolisers, and direct clinicians to safer or more effective analgesic options. A diagram illustrating the CPIC guideline for codeine is shown in Figure 1.

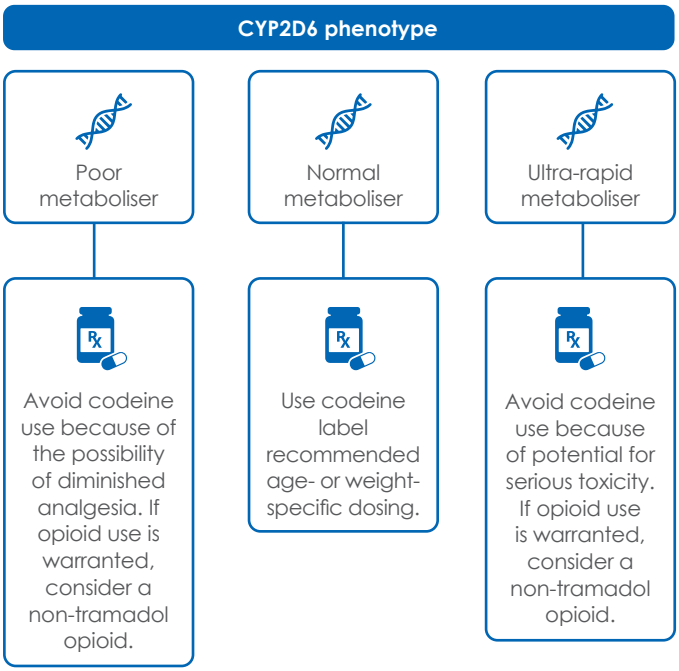


FIGURE 1: CYP2D6-CODEINE DOSING RECOMMENDATIONS

Genotype-directing dosing guidance is also available for several other opioids (including tramadol, morphine and fentanyl), as well as common non-steroidal anti-inflammatory drugs like ibuprofen, celecoxib and flurbiprofen.

Warfarin

Warfarin is still the most commonly used oral anticoagulant worldwide. Warfarin dosing is, however, notoriously challenging due to the drug's inherently narrow therapeutic index and large interpatient variability. Regular INR (International Normalised Ratio) monitoring is employed to determine the optimal warfarin dosage required for each patient. It often takes months of repeat INR-based dosage adjustments before this is achieved. Complications from inappropriate warfarin dosing are among the most frequently reported adverse events to the FDA, and one of the most common reasons for emergency room visits.

Warfarin is primarily metabolised by the CYP2C9, as well as VKORC1 and CYP4F2 enzymes, as shown in Figure 2. The *CYP2C9* gene has over 60 known variant alleles, with 18 of these associated with reduced enzyme function. While the *2 and *3 are the most common decreased function alleles observed in people of European ancestry, the *5, *6, *8 and *11 alleles are more common in those of African ancestry. Patients who inherit one or two of these reduced-function alleles are at greater risk of bleeding during warfarin therapy, and require lower doses to achieve similar levels of anticoagulation. The greatest potential benefit of PGT is prior to warfarin initiation or in the early stages of warfarin therapy.

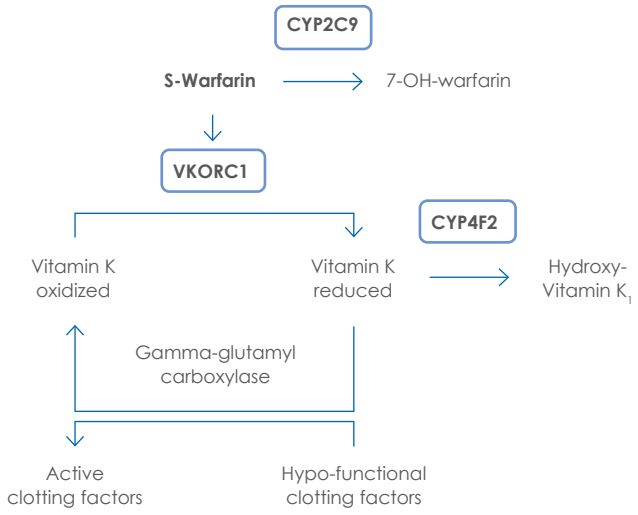


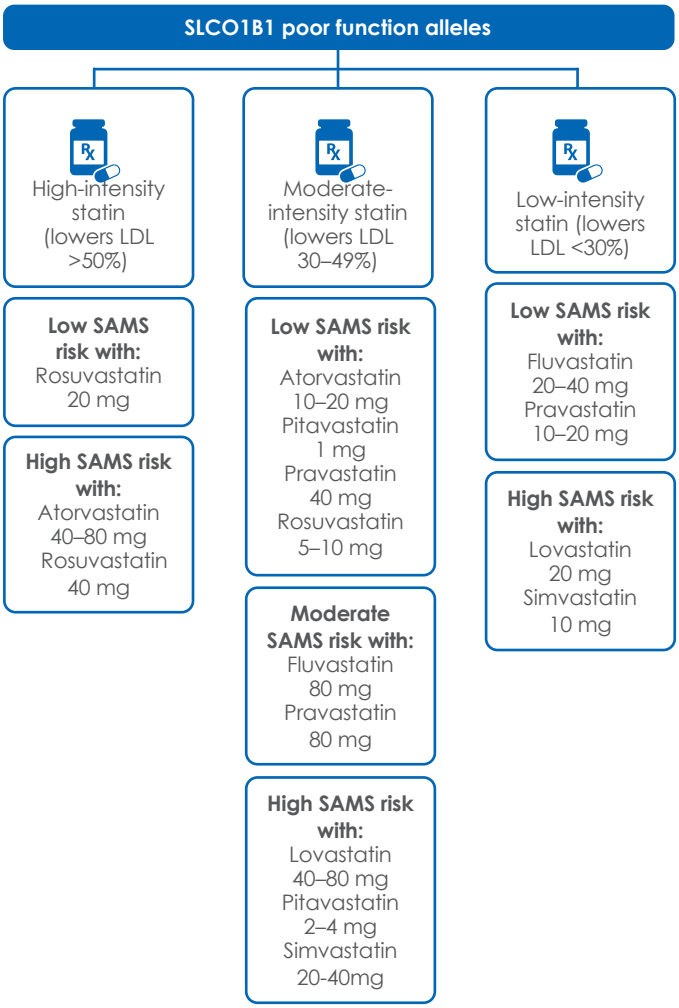
FIGURE 2: THE ENZYMES INVOLVED IN THE METABOLISM OF WARFARIN

Several genotype-based dosing guidelines are now available for use in clinical practice. *CYP2C9* gene-based warfarin dosing should, however, only be used in African patients if the *CYP2C9* *5, *6, *8 and *11 alleles were specifically tested for, in addition to the other common reduced-function alleles.

Statins

The statins are widely prescribed as a first-line therapy in the management of patients with acquired or inherited hypercholesterolaemia. As such, atorvastatin was reported to be the most commonly prescribed drug in the USA in 2018. The most commonly reported statin-related adverse drug reaction is statin-associated musculoskeletal symptoms (SAMS), which commonly manifest as myalgia, and less commonly as myopathy or even rhabdomyolysis. These painful musculoskeletal side effects impact adherence and ultimately reduce the long-term effectiveness of statin therapy.

Statins are metabolised in the liver by several enzymes, including SLCO1B1, ABCG2 and CYP2C9. Pharmacogenetic variants have been identified within these three genes, which affect enzyme function and can therefore be used to optimise statin dosing in patients who, genetically, may be at increased risk of SAMS. Genotype-based dosing guidelines are now available for most of the commonly prescribed statins, including simvastatin, atorvastatin and rosuvastatin. Figure 3 shows an example of dosage adjustment recommendations for SLCO1B1 poor function alleles from PharmGKB.



SAMS: Statin-associated musculoskeletal symptoms

FIGURE 3: SLCO1B1-STATIN DOSING RECOMMENDATIONS

Selective serotonin reuptake inhibitors

Selective serotonin reuptake inhibitors (SSRIs) are a first-line treatment option for major depressive and anxiety disorders. However, as many as 50% of patients do not respond to first-line therapy, leading to a significant increase in morbidity, as well as suicide risk. The CYP2C19 enzyme is intricately involved in the metabolism of several SSRIs, and polymorphisms within this gene can affect drug efficacy and safety. Individuals who are CYP2C19 poor metabolisers are exposed to much higher active drug levels, which can result in QT prolongation, as well as other less serious side effects, which may impact tolerance and adherence. Ultra-rapid metabolisers, on the other hand, will have lower plasma concentrations of these drugs, and therefore an increased probability of treatment failure. Genotype-based dosing recommendations for citalopram and escitalopram are shown in Figure 5. Guidelines are also available for other SSRIs, as well as selective noradrenaline reuptake inhibitors, tricyclic antidepressants and several antipsychotics.

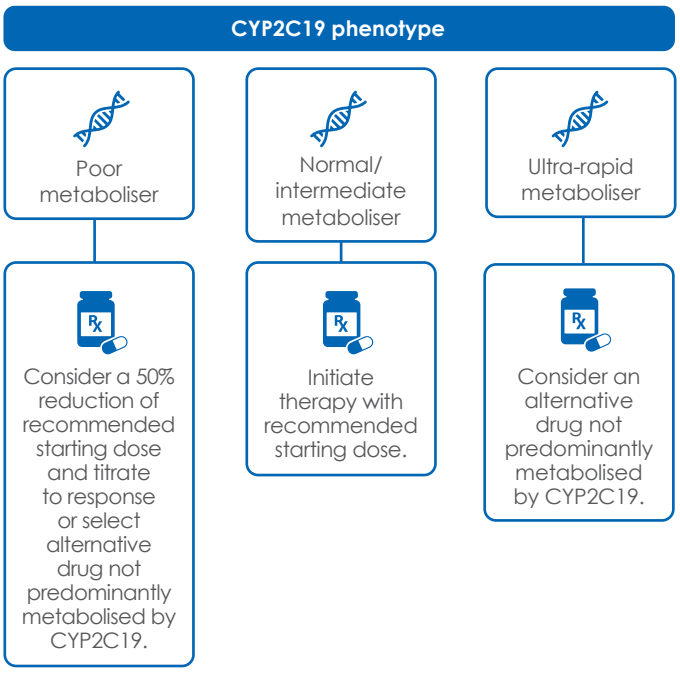


FIGURE 4: CYP2C19-CITALOPRAM DOSING RECOMMENDATIONS

Proton pump inhibitors

Proton pump inhibitors (PPIs) like omeprazole, lansoprazole and pantoprazole are commonly prescribed first-line agents used in the treatment of gastroesophageal reflux and peptic ulcer disease. Despite the overall effectiveness and safety of PPIs, some patients do not respond to treatment or develop treatment-related adverse events. Variability in PPI response has been attributed, in part, to genetic variation within the *CYP2C19* gene. Evidence now supports a clear association between CYP2C19 ultra-rapid

metaboliser status and the risk of treatment failure due to decreased plasma concentrations. Poor metabolisers, on the other hand, are at an increased risk of toxicity. *CYP2C19* genotyping can therefore help improve the efficacy and safety of PPI therapy. The clinical benefit of this was clearly shown in a recent meta-analysis, where the efficacy rates of PPIs in patients with reflux esophagitis and non-erosive reflux disease (NERD) differed significantly between different *CYP2C19* genotypes. An example of the CPIC guideline for omeprazole, lansoprazole, pantoprazole and dexlansoprazole is shown in Figure 5.

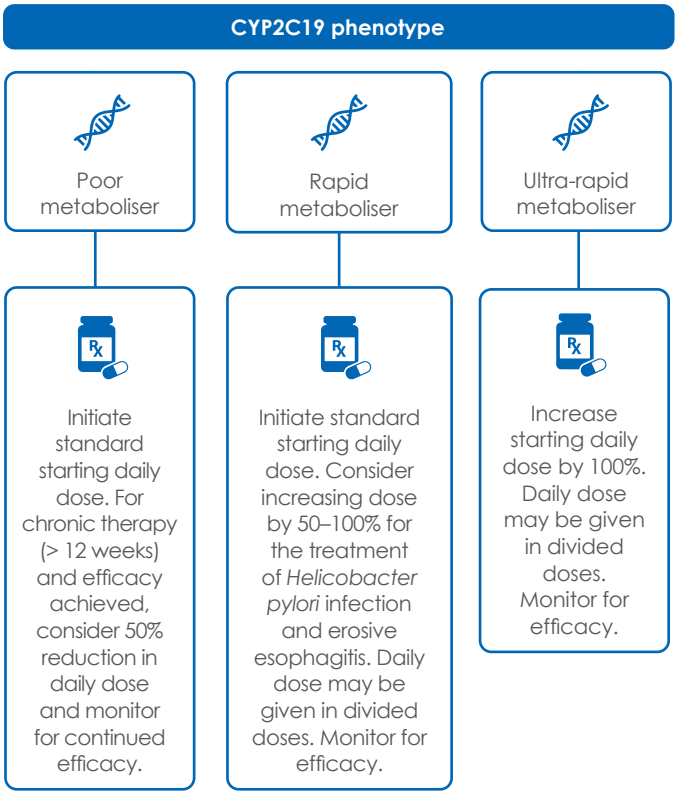


FIGURE 5: CYP2C19-PROTON PUMP INHIBITOR DOSING RECOMMENDATIONS

LIMITATIONS OF PHARMACOGENOMIC TESTING

As with any laboratory testing, it is important to be aware of the limitations of PGT to ensure that the information obtained can be meaningfully applied. Genomic variation within African population groups is notoriously diverse and these groups are still under-represented in most published pharmacogenomic research studies. The African Pharmacogenomics Consortium was established in 2018 in an attempt to actively bridge this gap. Most clinical laboratories, including Ampath, perform array-based genotyping, meaning that only known alleles or SNPs are tested for. If a patient has a rare allele or SNP not tested for, they will be defaulted to the *1 allele (which is the 'normal' or 'reference' version of the gene). Pharmacogenomic panels are not currently standardised and clinicians should be informed regarding which genes and alleles are included or omitted in order to select the most appropriate PGT panel for their patient. The evidence in support of various dosing recommendations differs and can change over time, as new evidence emerges. The level of evidence available should always be taken into account, and PGT should never be used blindly or in isolation when making decisions regarding clinical management in individual patients.

CONCLUSION

Genetic variation has been shown to play a major role in the inter-individual variability seen in response to many pharmacological agents. Harnessing each patient's unique genetic information can be a powerful tool in optimising and improving health outcomes for many common disorders. The field of pharmacogenomics is maturing, and evidence supporting its implementation into mainstream medicine is growing steadily, as is evidence for the cost-effectiveness and clinical value of panel-based PGT in many health care settings.

For more information, contact our pharmacogenomics specialists at **pgx@ampath.co.za.**

REFERENCES AVAILABLE ON REQUEST