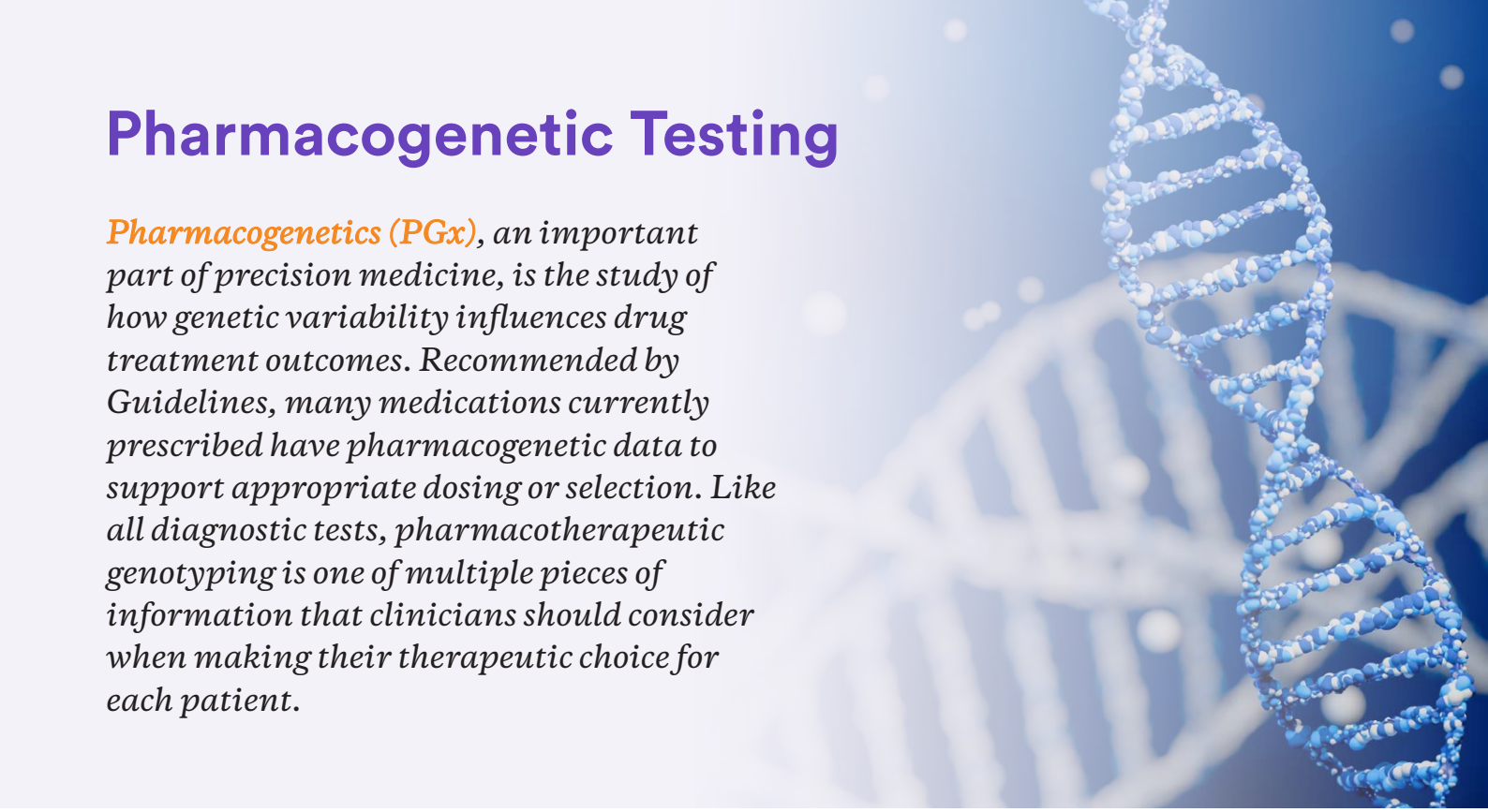
AUSTRALIAN Clinicallabs

Pharmacogenetic (PGx) Testing

Advanced insights for optimised drug treatment outcomes

Pharmacogenetic Testing



Pharmacogenetics (PGx), an important part of precision medicine, is the study of how genetic variability influences drug treatment outcomes. Recommended by Guidelines, many medications currently prescribed have pharmacogenetic data to support appropriate dosing or selection. Like all diagnostic tests, pharmacotherapeutic genotyping is one of multiple pieces of information that clinicians should consider when making their therapeutic choice for each patient.

Clinical Labs offers a comprehensive range of pharmacogenetic testing in order to provide Clinicians and Healthcare providers with important information to help decide on the most appropriate treatment for each individual, particularly in areas such as mental health, pain management, cardiology and oncology.

PGx test utility

Implementation of clinical pharmacogenetics, allele function and inferred phenotypes is a crucial step toward optimum patients' health. Identifying responders and non-responders to medications can reduce morbidity, avoid adverse events and optimise drug dosing.

Literature has shown that a large number of people are injured or die each year in hospitals from adverse drug events (ADEs), costing millions of dollars in healthcare costs each year. The field of genomic medicine presents one potential solution to reduce healthcare costs associated with ADEs and poor response to pharmacotherapy.

PGx guidelines

Evidence-based guidelines with pharmacotherapeutic recommendations for combinations of specific drugs and genotypes or predicted phenotypes are essential for implementing acquired pharmacogenetics knowledge in daily clinical practice.

The Dutch Pharmacogenetics Working Group (DPWG) and the Clinical Pharmacogenetics Implementation Consortium (CPIC) have been developing guidelines for more than a decade (Swen *et al.* 2011a; Caudle *et al.* 2017).

Recommendations are preferably made available at the time of drug prescribing and dispensing for a patient with a genotype that requires an action, such as a dose reduction (Swen *et al.* 2011a; Deneer and van Schaik, 2013).

When to order the test

Physicians may order the pharmacogenetic testing per drug at the point of care, or an alternative approach to ordering is the use of pre-emptive testing, perhaps as part of an annual exam in young adults or even children that require multiple treatments. As a result of the increasing number of drugs with pharmacogenetic data, the pre-emptive use of testing could significantly optimise drug outcomes (Schildcrout *et al.* 2012).

Regardless of when ordered (at time of treatment or prior), due to the continuing decline in the costs of genomic testing technologies, a broad-based pharmacogenetic screen may yield the greatest cost savings.

> *Identifying responders and non-responders to medications can reduce morbidity, avoid adverse events and optimise drug dosing.*

The *cytochrome P450 (CYP450)* and differences in drug metabolism

A family of enzymes (Figure 1), catalyses the metabolism of many drugs and xenobiotics. The genes that code for *cytochrome P450* enzymes are highly polymorphic, which can significantly affect drug metabolism in certain individuals. Differences in drug metabolism due to *CYP450* gene variants influence plasma levels of both the active drug and its metabolites.

For example, *CYP2D6, CYP2C19* and *CYP2C9* are responsible for the metabolism of a large number of commonly prescribed drugs, including warfarin, analgesics, clopidogrel, codeine, tamoxifen, some antidepressants, statins, proton pump inhibitors (PPIs) and anti-emetics (See Table 1). *CYP3A5* genotype results can be used to guide dosing of tacrolimus in organ transplant patients (Birdwell *et al*. 2015).

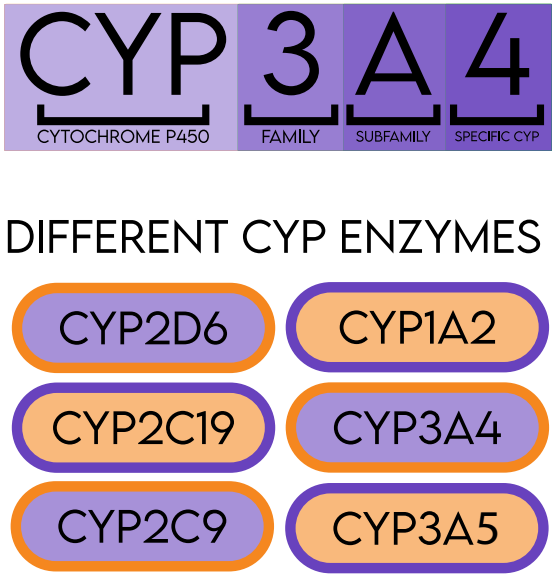


Figure 1. CYP Cytochrome P450 enzyme nomenclature and examples chart.

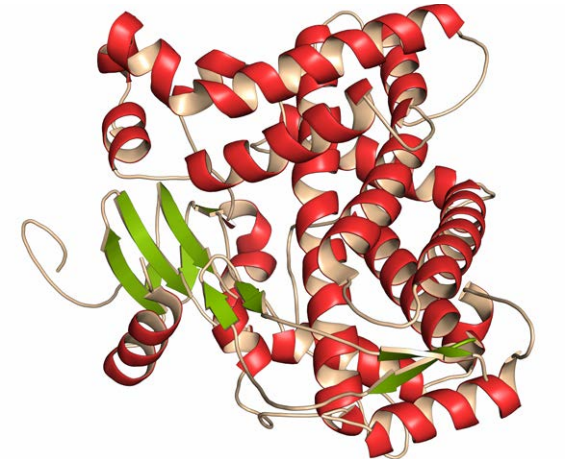


Figure 2. Cytochrome P450 (CYP2D6) liver enzyme in complex with a drug.

CYP2D6

CYP2D6 is the primary enzyme responsible for the metabolism of many commonly-used medications especially in mental health, oncology (tamoxifen and 5-HT3 receptor antagonists) (Goetz *et al*. 2018) and pain management (Crews *et al*. 2021) (Table 1 & Figure 2). *CYP2D6* is highly polymorphic with over 130 identified allelic variants and sub-variants identified (www.PharmVar.org; *CYP2D6* Allele Definition).

CYP2D6 alleles have been extensively studied in multiple geographically, racially, and ethnically diverse groups, and significant differences in allele frequencies have been observed. It is important to note that variation in *CYP2D6* may have implications for many therapies that may not be listed on this report (Gaedigk *et al*. 2017).

CYP2C19

The hepatic *CYP2C19* enzyme contributes to the metabolism of a large number of clinically relevant drugs such as antidepressants, benzodiazepines, mephenytoin, some proton pump inhibitors (Lima *et al*. 2021), and clopidogrel (Scott *et al.* 2013) and anti-fungal medication (voriconazole) (Moriyama *et al.* 2017) (Table 1). Like many other *CYP450* superfamily members, the *CYP2C19* gene is highly polymorphic, with >25 known variant alleles.

CYP2C9

Variants in the *CYP2C9* genes modify the rate at which some medications are metabolised. When considering antidepressant therapy such as tricyclic anti-depressants (TCAs), *CYP2C9* test is often combined with analysis of the *CYP2C19* and *CYP2D6* genes (Attia *et al.* 2014 and Hicks *et al.* 2017). When considering warfarin therapy, this test is often combined with analysis of *VKORC1.*

VKORC1 and *CYP2C9* and warfarin

Warfarin is one of the most commonly prescribed medications worldwide, used for many indications including prophylaxis and treatment of thromboembolic disorders, atrial fibrillation, or cardiac valve replacement, and systemic embolism after myocardial infarction (MI). Approved in the US in 1954, the high efficacy of warfarin is challenged by the high risk of ADEs due to its narrow therapeutic window, requiring careful monitoring and strict compliance.

While *CYP2C9* is predominantly involved in the metabolism of warfarin subtypes; *VKORC1* is the molecular target of the drug. In 2017, an international collaboration published an updated landmark paper defining appropriate warfarin doses based on a validated dosing algorithm of clinical biomarkers and *VKORC1/CYP2C9* genotypes (Johnson *et al*. 2017).

SLCO1B1 and statins

SLCO1B1 gene testing is clinically important in clearance of statins, especially simvastatin. Myopathy is reported in poor metabolisers of this gene. Alternative lipid lowering statins can be prescribed in lower doses such as atorvastatin, pravastatin and rosuvastatin (Ramsey *et al*. 2014).

Genetic variations can render some medications ineffective or toxic

Pharmacogenetic variants result in four distinct phenotypes: normal metabolisers (NMs), intermediate metabolisers (IMs), poor metabolisers (PMs), and ultrarapid metabolisers (UMs) which provides guidance to drug dosing and selection.

Overall, wild-type alleles are usually associated with functional enzyme-mediated metabolism. *Ultrarapid metabolisers* may not achieve therapeutic plasma levels due to decreased trough drug concentrations, whereas *poor metabolisers* treated with drugs that are metabolised by these enzymes are at increased risk for prolonged therapeutic effect or toxicity due to increased trough levels of therapeutic drugs.

Some anti-psychotic and SSRI medications can be contraindicated in intermediate *CYP2D6* metabolisers due to increased risk of adverse effects and so alternative agents must be prescribed.

CYP2D6 ultrarapid metabolisers treated with codeine exhibit symptoms of extreme sleepiness, confusion or shallow breathing; the lowest possible dose should be prescribed to these patients. Meanwhile, patients that are *CYP2D6 poor metabolisers* will not achieve sufficient pain control due to their inability to convert the drug to its active form of morphine (Crews *et al.* 2021).

CYP2C19 ultrarapid metabolisers should be prescribed alternative therapeutic agents other than benzodiazepines, such as citalopram (Celexa) and escitalopram (Lexapro) and TCAs such as impiramine (Tofranil) and clomipramine (Anafranil) due to possible decreases in the efficacy of these medications.

Pharmacogenetic markers in oncology

In addition to *RAS, BRAF, EGFR, ERBB2 (HER2), PK3CA* and *KIT* mutation and *PD-1, ROS, ALK* and *BCR-ABL* fusion genes, other genetic pharmacogenetic biomarkers play a role in patients' responses to oncology therapy.

UDP-glucuronosyltransferase gene (UGT1A1)

UGT1A1 is involved in the metabolism of *irinotecan* (Figure 3), a topoisomerase I inhibitor. *UGT1A1* gene polymorphism is associated with toxicity and clinical efficacy of irinotecan-based chemotherapy in patients with advanced solid tumours including colorectal, rectal and lung cancer (Fujii *et al.* 2019).

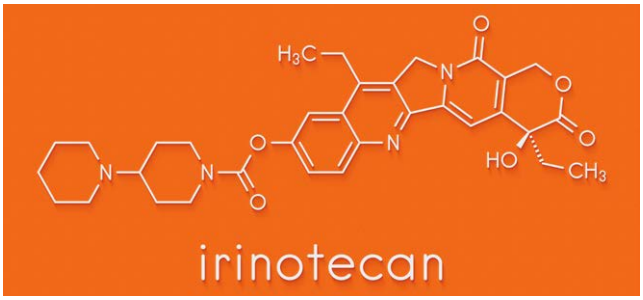


Figure 3. Irinotecan cancer chemotherapy drug molecule.

Thiopurine methyltransferase (TPMT)

TPMT is the primary enzyme responsible for thiopurine drugs (azathioprine, 6-mercaptopurine and 6-thioguanine) metabolism. These drugs are converted in the body to thioguanine nucleotides (TGNs).

Thiopurine therapy targets the replicating cells without overly harming normal cells. Several studies have established Single Nucleotide Polymorphisms (SNPs) in the *TPMT* gene that may lead to enzyme inactivity and therefore haematopoietic toxicity due to thiopurine drugs. It is recommended that physicians order *TPMT* genotyping before prescribing thiopurines to avoid bone marrow toxicity and consequent neutropenia (Relling *et al.* 2018).

Dihydropyrimidine dehydrogenase gene (DPYD)

DPD stands for dihydropyrimidine dehydrogenase, an enzyme made by the liver that breaks down uracil and thymine. The molecules created when pyrimidines are broken down (5,6-dihydrouracil and 5,6-dihydrothymine) are excreted by the body or used in other cellular processes. *DPYD* gene mutations result in excess quantities of the breakdown molecules in the blood, urine, and cerebrospinal fluid.

Mutations in the *DPYD* gene also interfere with the breakdown of drugs with structures similar to the pyrimidines, such as the cancer drugs 5-fluorouracil and capecitabine (two common chemotherapy drugs used as a treatment for a number of different cancers). As a result, these drugs accumulate in the body and cause the severe reactions and neurological manifestations as a result of DPD deficiency (Amstutz *et al.* 2017).

Conclusion

The incorporation of genetic information obtained from pharmacogenetic testing holds substantial promise to improve therapeutic decision making through improved efficacy and reduced adverse events. Considerations for clinical implementation, such as optimal laboratory workflows, electronic health record integration, and stakeholder engagement, as well as provider education, are crucial for patients' health.

PGx Testing at Clinical Labs

Comprehensive PGx Gene Panel:*

- *CYP2D6, CYP2C9, CYP2C19, CYP3A4, CYP3A5, CYP1A2, SLCO1B1* and *VKORC1*

Report: Our Comprehensive PGx Gene Panel report includes the genotype and the predicted phenotypes, such as the metaboliser status, along with potential drug-gene interaction and guidelines' recommendations. Please specify any medications of interest if you want them to be included in the report. The genes can be ordered separately or together. For individual genes, only genotyping/phenotyping will be reported.

Other Smaller PGx Genotyping Panels:**

- **Statins Predictor:** *SLCO1B1*
- **Warfarin Panel:** *CYP2C9* and *VKORC1*
- **Organ Transplant (Tacrolimus Immunosuppressant) PGx:** *CYP3A5*
- **PPIs PGx:** *CYP2C19*
- **Tamoxifen PGx:** *CYP2D6*
- **Clopidogrel PGx:** *CYP2C19*
- **Voriconazole Predictor:** *CYP2C19*
- **Anti-Psychotics Predictor:** *CYP2D6*
- **Anti-Depressants Predictor:** *CYP2D6* and *CYP2C19*

Single gene tests:**

- *TPMT* (Medicare rebate)
- *DPYD* (Medicare-rebatable from 1 November 2025)
- *UGT1A1*

To view the full list of drugs metabolised and genes tested, see Table 1 on page 7. For more information, including pricing, scan the QR code or visit clinicallabs.com.au/pharmacogenetictesting.

How to Order Pharmacogenetic (PGx) Testing at Clinical Labs

When to order: Before commencing therapy, or in cases of adverse reaction or resistance.

How to order: Fill out our routine Clinical Labs testing request form. List the gene(s) or group of genes required, and prescribed medications if available.

Collection locations: Patients can visit any of our 1,300+ convenient locations for their blood test. For locations, please visit clinicallabs.com.au/location.

Turnaround time: Results will be available 2-3 weeks after the sample receipt date.

Specimen required: 2x EDTA blood samples.

Report for smaller and single PGx gene panels:** You will receive an individual report indicating the genotype and predicted phenotypes for the ordered small gene panels or single gene(s), including metaboliser status and guideline recommendations where applicable. ****Comprehensive reports are only provided with our Comprehensive PGx Gene Panel*.

Test cost: Apart from the *TPMT* gene, Clinical Labs' PGx gene panels are non-Medicare rebatable (an out-of-pocket fee applies). The *DPYD* gene will be Medicare-rebatable from 1 November 2025. For more information, including pricing, visit clinicallabs.com.au/pharmacogenetictesting.

Depending on the PGx panel(s) ordered, testing may be performed and reported in collaboration with an external provider.

References:

Amstutz et al. 2017. Clin Pharmacol Ther
Attia et al. 2014. Chem Pharm Bull
Birdwell et al. 2015. Clin Pharmacol Ther
Caudle et al. 2017. Clin Pharmacol Ther
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Johnson et al. 2017. Clin Pharmacol Ther
Klein et al. 2009. N Engl J Med
Lima et al. 2021. Clin Pharmacol Ther
Moriyama et al. 2017. Clin Pharmacol Ther
Ramsey et al. 2014. Clin Pharmacol Ther
Relling et al. 2018. Clin Pharmacol Ther
Schildcrout et al. 2012. Clin Pharmacol Ther
Scott et al. 2013. Clin Pharmacol Ther
Swen et al. 2011a. Clin Pharmacol Ther

Table 1. Examples of drugs metabolised and genes tested

Medication	Gene(s)
Cardiology	
Carvedilol	*CYP2D6*
Clopidogrel	*CYP2C19*
Flecainide	*CYP2D6*
Metoprolol	*CYP2D6*
Warfarin	*VKORC1, CYP2C9*
Lipid Lowering Medication	
Atorvastatin	*SLCO1B1, CYP3A4*
Fluvastatin	*SLCO1B1, CYP2C9*
Lovastatin	*SLCO1B1*
Pitavastatin	*SLCO1B1*
Pravastatin	*SLCO1B1*
Rosuvastatin	*SLCO1B1*
Simvastatin	*SLCO1B1*
Gastroenterology	
Anti-Emetic	
Metoclopramide	*CYP2D6*
Ondansetron	*CYP2D6*
Tropisetron	*CYP2D6*
Proton Pump Inhibitors	
Esomeprazole	*CYP2C19*
Lansoprazole	*CYP2C19*
Omeprazole (Losec)	*CYP2C19*
Pantoprazole	*CYP2C19*
Rabeprazole	*CYP2C19*
Mental Health	
Anti-ADHD	
Atomoxetine	*CYP2D6*
Dextroamphetamine	*CYP2D6*
Lisdexamfetamine	*CYP2D6*
Anti-Depressants (MOAs)	
Moclobemide	*CYP2C19*
Anti-Depressants (SNRIs)	
Venlafaxine	*CYP2D6*
Anti-Depressants (SSRIs)	
Citalopram	*CYP2C19*
Escitalopram	*CYP2C19*
Fluoxetine (Prozac)	*CYP2D6*
Fluvoxamine	*CYP2D6*
Paroxetine	*CYP2D6*
Sertraline (Zoloft)	*CYP2C19*

Medication	Gene(s)
Mental Health	
Anti-Depressants (TCAs)	
Amitriptyline	*CYP2D6, CYP2C19*
Clomipramine	*CYP2D6, CYP2C19*
Desipramine	*CYP2D6, CYP2C19*
Dosulepin	*CYP2D6, CYP2C19*
Doxepin	*CYP2D6, CYP2C19*
Imipramine	*CYP2D6, CYP2C19*
Nortriptyline	*CYP2D6*
Trimipramine	*CYP2C19*
Anti-Depressants (Other)	
Vortioxetine	*CYP2D6*
Anti-Psychotics	
Aripiprazole	*CYP2D6*
Brexpiprazole	*CYP2D6*
Chlorpromazine	*CYP2D6*
Haloperidol	*CYP2D6*
Olanzapine	*CYP1A2*
Quetiapine	*CYP3A4*
Risperidone	*CYP2D6*
Zuclopenthixol	*CYP2D6*
Benzodiazepines (Anxiolytics)	
Clobazam	*CYP2C19*
Diazepam (Valium)	*CYP2C19*
Neurology	
Anti-Dementia	
Donepezil	*CYP2D6*
Galantamine	*CYP2D6*
Anti-Epileptics	
Phenytoin/ Fosphenytoin	*CYP2C9*
Multiple Sclerosis	
Siponimod	*CYP2C9*

Medication	Gene(s)
Oncology	
Atazanavir	*UGT1A1**
Azathioprine	*TPMT**
Belinostat	*UGT1A1**
Binimetinib	*UGT1A1**
Capecitabine	*DPYD**
Cisplatin	*TPMT**
Gefitinib	*CYP2D6*
Irinotecan	*UGT1A1**
Mercaptopurine	*TPMT**
Nilotinib	*UGT1A1*
Pazopanib	*UGT1A1**
Tamoxifen	*CYP2D6*
Tegafur	*DPYD**
Thioguanine	*TPMT**
5-Fluorouracil	*DPYD**
Organ Transplant	
Tacrolimus	*CYP3A5*
Pain Management	
NSAIDs	
Celecoxib	*CYP2C9*
Flurbiprofen	*CYP2C9*
Ibuprofen	*CYP2C9*
Piroxicam	*CYP2C9*
Meloxicam	*CYP2C9*
Opioids	
Codeine (prodrug)	*CYP2D6*
Dihydrocodeine	*CYP2D6*
Tramadol	*CYP2D6*
Urology	
Darifenacin	*CYP2D6*
Mirabegron	*CYP2D6*
Tamsulosin	*CYP2D6*
Tolterodine	*CYP2D6*
Anti-Fungal	
Voriconazol	*CYP2C19*

Please note that this is a guide for gene selection. Some specific medications may not be reported if they are listed under a drug class that is metabolised by the relevant gene.

*The following genes are not included in our Comprehensive PGx Gene Panel and need to be ordered individually: *UGT1A1, TPMT* and *DPYD*.

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ACLZBOH0070 ACLMAR-BF-INAT-0353.14 10/25