Overview of pharmacogenomic testing
Introduction

Pharmacogenomic testing includes the characterisation of clinically important genetic variants that affect drug metabolism. There are many genes that influence drug metabolism and since patients are commonly on more than one medication, the clinical consequences of genetic variations on drug metabolism may be complex.

The cytochrome P450 family of enzymes is important in first-pass drug metabolism in the liver. Their activity is mainly determined by genetic factors, although medications may also influence their activity. Individuals may carry genetic variants that result in rapid metaboliser status for some of these enzymes and weak metaboliser status for other enzymes. Most weak metabolisers are at risk of side-effects due to accumulation of the drug and active metabolites. In several important circumstances, weak metabolisers cannot convert inactive pro-drugs to active drug metabolites and may not derive adequate clinical benefit from the medication.

Since some immunological adverse drug reactions are restricted to certain HLA types, including severe cutaneous drug reactions, HLA typing may be appropriate prior to the initiation of certain medications.

Pharmacogenomic testing can be useful to assess whether a pro-drug will be likely to achieve the clinical benefit, by identifying individuals who are weak metabolisers. It may predict or explain which medications work best for individuals in whom previous drug treatments have not been effective or well-tolerated.

This testing can also help to identify individuals at risk of serious side effects, such as bone marrow suppression or serious cutaneous adverse reactions, from certain medications. In most circumstances, testing will be restricted to one or a few of the possible pharmacogenetic tests, although these results may have implications for other medications prescribed in the future.

Medicare reimbursement is generally not available for pharmacogenomic testing, with the exception of Thiopurine methyltransferase (TPMT) genotyping for patients being prescribed thiopurine drugs, including azathioprine, and HLA (tissue) typing for susceptibility to serious cutaneous drug reactions. Our pharmacogenomic and tissue-typing tests may be performed on dedicated peripheral blood EDTA specimens or on buccal swab DNA collector specimens. Since most pharmacogenomic testing is performed prior to, or soon after, initiation of new medications, results from these complex tests are usually available within two weeks.

In this document, we describe our pharmacogenetic testing menu, include a summary of the clinical utility for the most common test circumstances and provide patient information. This testing allows us to advise doctors whether their patient’s medication, likely to be taken for a long period of time for a significant illness, will be effective, as well as likely to be safe for the patient to take.

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Our testing menu

Our current pharmacogenetic testing menu includes validated assays for the cytochrome P450 enzymes 2D6, 2C19, 2C9/VKORC1; the glucuronidation enzyme, UGT1A1; dihydro-pyrimidine dehydrogenase, DPYD; and thiopurine methyltransferase, TPMT. The tissue typing tests we offer that have relevance to serious cutaneous adverse reactions include HLA-B*15:02, HLA-B*57:01 and HLA-B*58:01. Concurrent profiling CYP2D6, CYP3A4 and CYP3A5 allows algorithm refined guidance for pain management and psychotropic drugs.

<table>
<thead>
<tr>
<th>Test</th>
<th>Clinical utility</th>
<th>Medicare</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6</td>
<td>Will tamoxifen be effective? Will codeine or tramadol be effective? Will tricyclic antidepressants be tolerated?</td>
<td>N</td>
</tr>
<tr>
<td>CYP2D6, 3A4, 3A5</td>
<td>Will fentanyl or methadone be tolerated? Which analgesics and anti-psychotics will be tolerated?</td>
<td>N</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Will clopidogrel be effective? Will tricyclic antidepressants be tolerated?</td>
<td>N</td>
</tr>
<tr>
<td>CYP2C9/VKORC1</td>
<td>What is optimal warfarin dose?</td>
<td>N</td>
</tr>
<tr>
<td>TPMT</td>
<td>Will azathioprine or 6-mercaptopurine be safe?</td>
<td>Y</td>
</tr>
<tr>
<td>UGT1A1</td>
<td>Will irinotecan be safe?</td>
<td>N</td>
</tr>
<tr>
<td>DPYD</td>
<td>Will 5-fluorouracil, capecitabine or tegafur be safe?</td>
<td>N</td>
</tr>
<tr>
<td>HLA-B*15:02</td>
<td>Will carbamazepine be safe?</td>
<td>Y</td>
</tr>
<tr>
<td>HLA-B*57:01</td>
<td>Will abacavir be safe?</td>
<td>Y</td>
</tr>
<tr>
<td>HLA-B*58:01</td>
<td>Will allopurinol be safe?</td>
<td>Y</td>
</tr>
</tbody>
</table>
CYP2D6 pharmacogenomics

Sufficient activity of CYP2D6 is necessary for the conversion of some inactive pro-drugs to active drug metabolites, in the case of tamoxifen to endoxifen and, similarly, for codeine to morphine. CYP2D6 poor metabolisers may not get the desired clinical benefit from these medications. For many other drugs, insufficient activity of CYP2D6 may not allow the breakdown of active drugs to inactive metabolites. There is the potential for drug toxicity in CYP2D6 poor metabolisers with tricyclic antidepressants, some other psychoactive medications and some cardiovascular drugs. Some medications are metabolised by enzymes other than CYP2D6 and, for those medications, there are no recommendations for dosage changes according to CYP2D6 status.

Well-documented guidelines have been published for dosage reduction of the tricyclic antidepressants, amitryptiline and nortryptiline, in CYP2D6 poor metabolisers. Similar principles apply for the other tricyclic antidepressants: clomipramine, desipramine, doxepin, imipramine and trimipramine. In CYP2D6 poor metabolisers, dosage reduction or alternative agents are recommended for sedative medications, like haloperidol and propafenone, and for both the beta-blocker, metoprolol, and the anti-arrhythmic, flecainide.

At present, there are no recommendations for dosage modification for SSRI antidepressants, including olanzapine, mirtazapine, clozapine, duloxetine, fluoxetine, paroxetine. No dose modification is recommended for risperidone or zuclopenthixol or atomoxetine. No dosage reduction is recommended for the beta-blocker, carvedilol.

Tamoxifen (CYP2D6) pharmacogenomics

Tamoxifen is a pro-drug anti-oestrogen agent used to treat and prevent breast cancer. Initially, tamoxifen is metabolised in the liver to N-desmethyl-tamoxifen or 4-hydroxy-tamoxifen and then to endoxifen.

The clinical effectiveness of tamoxifen is dependent on its activation to endoxifen, an active metabolite by the cytochrome P450 (CYP) system, principally CYP2D6. Poor and intermediate metabolisers may not generate enough endoxifen for effective anti-oestrogen effect.

The Sonic Genetics Tamoxifen CYP2D6 assay defines your patient as either normal (wild-type, i.e. ultrarapid or extensive metaboliser), for whom normal dosing and therapeutic effectiveness of tamoxifen should occur, or as an intermediate or poor metaboliser, for whom alternative therapies like aromatase inhibitors should be considered.

<table>
<thead>
<tr>
<th>Phenotype (Genotype)</th>
<th>Implications for tamoxifen</th>
<th>Therapeutic recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extensive metabolisers (EM): carry two active alleles (*1, *2)</td>
<td>Predicts good clinical effect</td>
<td>Standard dosage</td>
</tr>
</tbody>
</table>

The Sonic Genetics Tamoxifen CYP2D6 assay defines your patient as either normal (wild-type, i.e. ultrarapid or extensive metaboliser), for whom normal dosing and therapeutic effectiveness of tamoxifen should occur, or as an intermediate or poor metaboliser, for whom alternative therapies like aromatase inhibitors should be considered.

There is no Medicare reimbursement for this test.

<table>
<thead>
<tr>
<th>Name</th>
<th>Utility</th>
<th>Specimen</th>
<th>Result time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen 2D6</td>
<td>Will tamoxifen be effective?</td>
<td>EDTA</td>
<td>1-2 weeks</td>
</tr>
</tbody>
</table>
CYP2D6 pharmacogenomics

Patient information

The cytochrome P450 (CYP) protein family is a group of enzymes important for the metabolism of several drugs. One member of this family is the CYP2D6 protein, which is encoded by the CYP2D6 gene. This test identifies whether the two copies (alleles) of the CYP2D6 gene you carry make you likely to be a normal, reduced (intermediate) or weak metaboliser of medications processed by CYP2D6.

Some medications are ‘pro-drugs’, which require metabolism to generate an active form of the drug. CYP2D6 weak metabolisers may not process enough of the pro-drug to get the intended benefit of the medication. An important example of a pro-drug is tamoxifen. CYP2D6 weak metabolisers may not make enough of the active metabolite (endoxifen) for adequate anti-oestrogen effect. Another example of a pro-drug is codeine, which must be metabolised to the active metabolite, morphine. This test allows your doctor to advise you as to whether tamoxifen will be effectively metabolised to an active drug. Similarly, this test allows your doctor to determine whether codeine will be likely to be an effective form of pain relief for you.

Other medications are ‘active’ drugs, for which metabolism by CYP2D6 is important in their breakdown to inactive forms. Tricyclic antidepressants are an example of these active drugs that are processed by CYP2D6, such that CYP2D6 weak metabolisers may require reduced doses of these medications. This test allows your doctor to advise you as to whether tricyclic antidepressants are likely to be safe and tolerated.

In interpreting your pharmacogenomic test results, your doctor will consider your medical history, your other medications and the clinical problem relevant to the test. The laboratory will provide support to your doctor, if needed, but will not advise patients directly about their medications.
Clopidogrel (CYP2C19) pharmacogenomics

Clopidogrel is an anti-platelet agent, used to reduce atherosclerotic events (such as myocardial infarction, stroke and peripheral vascular disease) in patients with atherosclerosis documented by recent vascular events.

CYP2C19 poor and intermediate metabolisers may not generate enough active clopidogrel metabolite for adequate anti-platelet effect, especially in patients who have had recent coronary artery stents. Consider alternate treatment or treatment strategies in patients identified as CYP2C19 poor metabolisers.

<table>
<thead>
<tr>
<th>Phenotype (Genotype)</th>
<th>Implications for clopidogrel</th>
<th>Therapeutic recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultra-rapid metaboliser (UM): carry at least one gain-of-function allele (*1/*17, *17/*17)</td>
<td>Normal (EM) or increased (UM) platelet inhibition; normal (EM) or decreased (UM) residual platelet aggregation</td>
<td>Clopidogrel label-recommended dosage and administration</td>
</tr>
<tr>
<td>Extensive metaboliser (EM): carry two active alleles (*1/*1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate metaboliser (IM): carry at least one inactive allele (*1/*2, *1/*3, *17/*2, *17/*3)</td>
<td>Reduced platelet inhibition; increased residual platelet aggregation</td>
<td>Prasugrel or other alternative therapy (if no contraindication)</td>
</tr>
<tr>
<td>Poor metaboliser (PM): carry two inactive alleles (*2/*2, *2/*3, *3/*3)</td>
<td>Significantly reduced platelet inhibition; increased residual platelet aggregation</td>
<td>Prasugrel or other alternative therapy (if no contraindication)</td>
</tr>
</tbody>
</table>

The Sonic Genetics Clopidogrel CYP2C19 assay defines your patient as either normal (wild-type, i.e. ultrarapid or extensive metaboliser), for whom normal dosing and therapeutic effectiveness of clopidogrel should occur, or as an intermediate or poor metaboliser, for whom alternative therapies, such as prasugrel, should be considered.

There is no Medicare reimbursement for this test.

<table>
<thead>
<tr>
<th>Name</th>
<th>Utility</th>
<th>Specimen</th>
<th>Result time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel 2C19</td>
<td>Will clopidogrel be effective?</td>
<td>EDTA</td>
<td>1-2 weeks</td>
</tr>
</tbody>
</table>

CYP2C19 pharmacogenomics

Patient information

The cytochrome P450 (CYP) protein family is a group of enzymes important for the metabolism of several drugs. One member of this family is the CYP2C19 protein, which is encoded by the CYP2C19 gene. This test identifies whether the two copies (alleles) of the CYP2C19 gene you carry make you likely to be a normal, reduced (intermediate) or weak metaboliser of medications processed by CYP2C19.

Some medications are ‘pro-drugs’, which require some metabolism to generate an active form of the drug. CYP2C19 weak metabolisers may not process enough of the pro-drug to get the intended benefit of these medications. An example of such a pro-drug is clopidogrel (Iscover or Plavix). CYP2C19 weak metabolisers may not make enough active drug metabolites to get sufficient blood-thinning effect (anti-platelet activity), while CYP2C19 ultra-rapid metabolisers may get too much blood thinning. This test allows your doctor to determine whether clopidogrel is likely to be effective for you.

Other medications are ‘active’ drugs, for which metabolism by CYP2C19 is important in their breakdown to inactive forms. Examples of these active drugs are the tricyclic antidepressants, for which CYP2C19 weak metabolisers should have a 50% dose reduction. Another example relates to the use of proton-pump inhibitors, for which CYP2C19 ultra-rapid metabolisers may not get as much benefit, especially when used in combination treatments for eradication of Helicobacter from their stomach.

In interpreting your pharmacogenomic test results, your doctor will consider your medical history, your other medications and the clinical problem relevant to the test. The laboratory will provide support to your doctor, if needed, but will not advise patients directly about their medications.
Warfarin (CYP2C9/VKORC1) pharmacogenomics

Warfarin is a racemic mixture of the more potent S-Warfarin and less potent R-Warfarin. Warfarin inhibits the vitamin K-epoxide reductase complex (VKORC1), which limits the availability of active vitamin K and reduces the generation of active clotting factors. Most warfarin is metabolised by CYP2C9 to inactive metabolites, so genetic variants of CYP2C9 with less activity result in a greater warfarin activity for a given dose. Similarly, genetic variants of VKORC1 with less activity result in reduced generation of active clotting factors.

The VKORC1:c.-1639G>A variant is associated with lower dose requirements for warfarin in Caucasians and Asians. Increased bleeding risk and lower initial dose requirements have been associated with the CYP2C9*2 and CYP2C9*3 alleles. Most of the variability in warfarin dose between individuals results from genetic variation in VKORC1 and CYP2C9, as well as age, height, body weight and interacting drugs. A dosage algorithm that combines these variables is available at www.warfarindosing.org

The clinical utility of this test is prior to and within the first month of warfarin therapy to guide dosage. Laboratory testing may be useful (for patients in whom there is marked INR volatility).

Table 1: Recommended daily warfarin doses (mg/day) to achieve a therapeutic INR based on CYP2C9 and VKORC1 genotype using the warfarin product insert approved by the United States Food and Drug Administration.

<table>
<thead>
<tr>
<th>VKORC1 Genotype (c.-1639G&gt;A, rs9923231)</th>
<th>CYP2C9*1/*1</th>
<th>CYP2C9*1/*2</th>
<th>CYP2C9*1/*3</th>
<th>CYP2C9*2/*2</th>
<th>CYP2C9*2/*3</th>
<th>CYP2C9*3/*3</th>
</tr>
</thead>
<tbody>
<tr>
<td>GG</td>
<td>5-7</td>
<td>5-7</td>
<td>3-4</td>
<td>3-4</td>
<td>3-4</td>
<td>0.5-2</td>
</tr>
<tr>
<td>GA</td>
<td>5-7</td>
<td>3-4</td>
<td>3-4</td>
<td>3-4</td>
<td>0.5-2</td>
<td>0.5-2</td>
</tr>
<tr>
<td>AA</td>
<td>3-4</td>
<td>3-4</td>
<td>0.5-2</td>
<td>0.5-2</td>
<td>0.5-2</td>
<td>0.5-2</td>
</tr>
</tbody>
</table>

The Sonic Genetics Warfarin CYP2C9/VKORC1 assays identify genetic variants for which lower doses of warfarin should be considered.

There is no Medicare reimbursement for this test.

Name | Utility | Specimen | Result time
--- | --- | --- | ---
2C9/VKORC1 | Estimate warfarin dosing | EDTA | 1-2 weeks

Warfarin (CYP2C9/VKORC1) pharmacogenomics

Patient information

Warfarin works to ‘thin’ the blood by reducing the production of clotting factors that depend on Vitamin K for their production. Specifically, warfarin inhibits an enzyme called VKORC1, which limits the availability of active vitamin K that is necessary for the production of these clotting factors.

The cytochrome P450 (CYP) protein family is a group of enzymes important for the metabolism of several drugs. One member of this family is the CYP2C9 protein, which is encoded by the CYP2C9 gene. Most warfarin is processed by CYP2C9 to inactive metabolites so genetic variants which cause a CYP2C9 enzyme with less activity will result in a greater warfarin effect for a given dose.

Similarly, genetic variants of VKORC1 with less activity result in reduced generation of active clotting factors.

A genetic variation in the promoter region of the VKORC1 gene, called the c.-1639G>A variant, is associated with lower dose requirements for warfarin in Caucasians and Asians. The genetic variations in CYP2C9 called CYP2C9*2 and CYP2C9*3 cause less efficient processing of warfarin and so increase bleeding risk and lower the initial dose requirements. Everyone carries two copies (alleles) of the CYP2C9 gene and may inherit any combination of CYP2C9 variants. Therefore, a person may have either two normal copies or one normal and one less active copy or two less active copies, with each combination having progressively less enzyme activity and so a greater warfarin effect.

A computer algorithm that predicts your likely warfarin dose, which takes into account your VKORC1 and 2C9 genotype along with your age, height, body weight and other variables, is available at www.warfarindosing.org

In interpreting your pharmacogenomic test results, your doctor will consider your medical history, your other medications and the clinical problem relevant to the test. The laboratory will provide support to your doctor, if needed, but will not advise patients directly about their medications.
TPMT pharmacogenomics

Azathiopurine and 6-mercaptopurine are thiopurine drugs that are metabolised by thiopurine methyl transferase (TPMT). They are most commonly used as steroid-sparing immunosuppressive drugs to treat inflammatory bowel disease, autoimmune disorders and severe eczema. In the past, they have been used to provide transplant immunosuppression, while 6-mercaptopurine has also been used for treating cancers. The approach to dosing adjustments based on TPMT status may differ, depending on the clinical need to initiate therapy with higher starting doses.

Determination of TPMT status can allow safer and faster dose escalation. Approximately 0.3% (1:300) of patients have two non-functional alleles (homozygous-deficient) of the TPMT gene and have little or no detectable enzyme activity and, if given usual doses, can accumulate excessive cellular concentrations of active thioguanine nucleotides, predisposing them to toxicity with profound myelosuppression. Some adverse reactions to azathioprine or 6-mercaptopurine (including pancreatitis) are a consequence of other genetic mechanisms and cannot be predicted by this test.

<table>
<thead>
<tr>
<th>Phenotype (Genotype)</th>
<th>TPMT allele combinations</th>
<th>Therapeutic recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal, high activity (two functional alleles)</td>
<td>*1/*1</td>
<td>Start with normal starting dose. Allow 2 weeks to reach steady state after each dose adjustment.</td>
</tr>
<tr>
<td>Intermediate activity (one functional plus one non-functional allele)</td>
<td>*1/*2, *1/*3A, *1/*3B, *1/*3C</td>
<td>Start with reduced doses (start at 30-70%) and adjust doses based on degree of myelosuppression and disease specific guidelines. Allow 2-4 weeks to reach steady state</td>
</tr>
</tbody>
</table>

The Sonic Genetics TPMT assay defines your patient as either a normal (wild-type or rapid) metaboliser, for whom normal dosing and therapeutic effectiveness of azathioprine or 6-mercaptopurine should occur, or as an intermediate metaboliser, for whom reduced doses should be considered, or as a poor metaboliser, for whom alternative therapies should be considered.

This test is Medicare rebatable.

<table>
<thead>
<tr>
<th>Name</th>
<th>Utility</th>
<th>Specimen</th>
<th>Result time</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPMT</td>
<td>Are azathioprine and 6-mercaptopurine safe?</td>
<td>EDTA</td>
<td>1-2 weeks</td>
</tr>
</tbody>
</table>

TPMT pharmacogenomics

Patient information

Thiopurine methyltransferase (TPMT) protein, which is encoded by the TPMT gene, is an enzyme involved in the breakdown of several drugs. Sufficient TPMT enzyme activity is necessary for the breakdown of active drug to its inactive metabolites. This test identifies whether the two copies (alleles) of this gene you carry make you likely to be a normal, intermediate (decreased) or weak (deficient) metaboliser of azathioprine or 6-mercaptopurine, the main medications processed by TPMT. Only some medications are metabolised by TPMT.

Normal metabolisers have two active copies of the TPMT gene, intermediate metabolisers have one active copy and one non-functional copy, while weak metabolisers have two non-functional copies. Your doctor may consider a dose reduction of drugs processed by TPMT for intermediate metabolisers, while alternative medications should be considered for weak metabolisers.

Weak metabolisers of azathioprine and 6-mercaptopurine may develop potentially very serious bone marrow suppression, with very low white cell counts. This test greatly reduces the risk of this side effect from these medication at higher doses. Other adverse effects from these medications that may occur are not related to your TPMT activity.

In interpreting your pharmacogenomic test results, your doctor will consider your medical history, your other medications and the clinical problem relevant to the test. The laboratory will provide support to your doctor, if needed, but will not advise patients directly about their medications.
UGT1A1 pharmacogenomics

UDP glucuronosyltransferase 1 family, polypeptide A1 (UGT1A1), is a uridine diphosphate glucuronosyltransferase. It is an important enzyme in the hepatic glucuronidation pathway, which converts bilirubin, drugs, hormones and steroids into water-soluble molecules that can be excreted in the bile. Pathogenic genetic variations in UGT1A1 are associated with Gilbert’s syndrome and Crigler-Najjar syndrome, which usually present with jaundice, due to raised unconjugated bilirubin. In cancer patients being treated with irinotecan, severe drug toxicity may occur, due to deficiency of UGT1A1.

Safe dosing of irinotecan can be established by genotyping UGT1A1. If a dose of irinotecan of more than 250 mg/m² is to be administered and patient is homozygous for the deficient allele (*28/*28), then the initial dose of irinotecan should be reduced by 30% and can be increased according to white cell count tolerance.

There is no Medicare reimbursement for this test.

<table>
<thead>
<tr>
<th>Name</th>
<th>Utility</th>
<th>Specimen</th>
<th>Result time</th>
</tr>
</thead>
<tbody>
<tr>
<td>UGT1A1</td>
<td>Will irinotecan be safe? Does the patient have Gilbert’s or a Crigler-Najjar syndrome?</td>
<td>EDTA</td>
<td>1-2 weeks</td>
</tr>
</tbody>
</table>

UGT1A1 pharmacogenomics

Patient information

The UGT1A1 protein is an important liver enzyme in the conversion of certain compounds into water-soluble molecules so they can be excreted from the body. The UGT1A1 protein is encoded by the UGT1A1 gene. This test identifies whether the two copies (alleles) of the UGT1A1 gene you carry make you a weak metaboliser of irinotecan. Persons with two copies of a variant allele, called UGT1A1*28, should have reduced doses of this medication and be carefully monitored with laboratory tests (blood count) during treatment. At this time, this test is not used for predicting tolerance of other medications, but it can be used to confirm a diagnosis of disorders with elevated bilirubin levels, including Gilbert’s syndrome and Crigler-Najjar syndrome.

In interpreting your pharmacogenomic test results, your doctor will consider your medical history, your other medications and the clinical problem relevant to the test. The laboratory will provide support to your doctor, if needed, but will not advise patients directly about their medications.
DPYD pharmacogenomics

The DPYD gene encodes for dihydropyrimidine dehydrogenase (DPD), which is the initial and rate-limiting enzyme in the catabolism of uracil and thymidine. Since this enzyme degrades fluoropyrimidines, including important oncology drugs (5-fluorouracil, capecitabine and tegafur), DPYD genetic variations that impair DPD function greatly increase the risk of fatal toxicity from these agents. Individuals inherit two alleles and usually both DPYD alleles express DPD protein. Genetic variations in these DPYD alleles result in either normal activity, decreased activity or inactivity of the encoded DPD protein as designated by the nomenclature below:

- **Active Alleles**: *1, *4, *5, *6, *9A
- **Decreased activity Alleles**: *9B, *10

Individuals may be normal, intermediate or poor metabolisers of fluoropyrimidine drugs, depending on which DPYD gene variants they have inherited. Poor metabolisers have either two inactive alleles, or two decreased activity alleles or one inactive and one decreased activity allele. Such patients should not be administered any fluoropyrimidine medications. Intermediate metabolisers have one active and either one decreased activity or inactive allele; they may tolerate a 50% dose reduction for 5-fluorouracil or capecitabine, but there is no dosage recommendation for tegafur in this setting at this time.

The Sonic Genetics DYPD assay defines your patient either as normal (wild-type or normal metaboliser), for whom normal dosing and therapeutic effectiveness should occur, or as an intermediate metaboliser, for whom dosage reduction should be considered, or as a poor metaboliser for whom these medications should not be given.

**There is no Medicare reimbursement for this test.**

<table>
<thead>
<tr>
<th>Name</th>
<th>Utility Specimen</th>
<th>Result time</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPYD</td>
<td>Are 5-FU, capecitabine or tegafur safe?</td>
<td>EDTA</td>
</tr>
</tbody>
</table>

### DPYD pharmacogenomics

**Patient information**

The DPD protein, encoded by the DPYD gene, is an enzyme involved in the breakdown of several important cancer drugs. Genetic variations in the DPYD gene, that result in impaired DPD enzyme function, greatly increase the risk of fatal toxicity from these drugs. Sufficient DPD activity is necessary for the breakdown of active drug to its inactive metabolites. This test identifies whether the two copies (alleles) of this gene you carry make you likely to be a normal, intermediate (decreased) or weak metaboliser of medications processed by DPD. Only some medications are metabolised by DPD.

Normal metabolisers have two active copies of the DPYD gene, while intermediate metabolisers have one active and either one decreased activity allele or an inactive copy of the DPYD gene. Weak metabolisers have either two inactive copies, two decreased activity copies or one inactive and one decreased activity copy of the DPYD gene.

The clinically important medications processed by DPD include 5-fluorouracil (5-FU), capecitabine and tegafur. Your doctor may consider a dose reduction of these drugs for intermediate metabolisers, while alternative medications may be considered for weak metabolisers.

In interpreting your pharmacogenomic test results, your doctor will consider your medical history, your other medications and the clinical problem relevant to the test. The laboratory will provide support to your doctor, if needed, but will not advise patients directly about their medications.
HLA-B*15:02; HLA-B*57:01; HLA-B*58:01

Tissue typing for severe cutaneous adverse reactions

Some adverse drug reactions are immunologically mediated through the binding of CD8 or CD4 T cells to drug-bound cells bearing MHC class I or class II molecules. These very serious adverse drug reactions may affect the skin, the liver or other organs. As these effects are limited to a set of (MHC) tissue types, detecting these susceptible tissue types gives clinicians the opportunity to avoid exposing patients to these uncommon but life-threatening severe adverse cutaneous drug reactions. It is thought that almost all persons with HLA-B*57:01 prescribed abacavir will develop a serious adverse reaction. Many persons of Chinese ethnicity will develop severe cutaneous adverse reactions to carbamazepine if they have the HLA-B*15:02 allele or allopurinol if they carry the HLA-B*58:01 allele. The predictive value of these tissue types for avoiding serious adverse reactions varies with each medication and may be dissimilar for persons of different ethnicity. At present, tissue typing prior to commencement of medications has clinical utility for the following circumstances:

HLA-B*15:02 (sometimes HLA-A*31:01) and carbamazepine safety

The risk of severe cutaneous adverse reactions to carbamazepine is mostly restricted to persons of Chinese or Asian ancestry who are heterozygous or homozygous for HLA-B*15:02.

HLA-B*57:01 and abacavir safety

The risk of severe cutaneous adverse reactions to abacavir is strongly associated with either heterozygosity or homozygosity for HLA-B*57:01. Regardless of ethnicity, HLA genotyping should be undertaken prior to commencement of this medication.

HLA-B*58:01 and allopurinol safety

The risk of severe cutaneous adverse reactions to allopurinol is greatly increased in Chinese and Thai persons, as well as Koreans (with renal impairment), if they are heterozygous or homozygous for HLA-B*58:01. HLA genotyping should be considered prior to commencement of allopurinol.

This test is Medicare rebatable.

<table>
<thead>
<tr>
<th>Name</th>
<th>Utility</th>
<th>Specimen</th>
<th>Result time</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA tissue typing</td>
<td>Are carbamazepine, abacavir or allopurinol safe?</td>
<td>EDTA</td>
<td>1-2 weeks</td>
</tr>
</tbody>
</table>

Tissue typing and severe cutaneous adverse reactions

Patient information

Your doctor has requested a tissue-typing test to determine whether you are at risk of a serious cutaneous adverse reaction to a medication, due to an inappropriate immune response. Not all persons with a particular tissue type gene will necessarily have such a reaction, although persons with HLA-B*57:01 should never take the anti-retroviral abacavir. If you have already been taking carbamazepine or allopurinol for more than three months and have not yet had an adverse reaction, you are unlikely to be affected, even if the test detects an at-risk genotype (HLA-B*15:02 or HLA-B*58:01).

This testing does not exclude the risk of other forms of adverse immune-mediated drug reactions, including allergic reactions. In interpreting your tissue-typing results, your doctor will consider your medical history, your other medications and the clinical problem relevant to the test. The laboratory will provide support to your doctor, if needed, but will not advise patients directly about their medications.

For further information please contact Sonic Genetics on 1800 010 447. If you would like to discuss a patient, or a patient’s results, Dr Karl Baumgart (9855 5286) and Dr Scott Mead (9855 6276) welcome your calls.
Sonic Healthcare is an established global pathology company, with practices and laboratories across the US, Europe and Australasia. Sonic Genetics harnesses this worldwide expertise, wherever it happens to be, in order to provide doctors and patients with the widest possible ranges of genetic and molecular testing.

By co-ordinating our international resources, we can offer cost-effective, global access to the full range of genetic testing. We offer thousands of tests, and our international reputation ensures that we provide the highest possible quality, while remaining firmly committed to operating at the forefront of this evolving area of medicine.

DR KARL BAUMGART  BSc (Med), MB, BS, PhD, FRACP, FRCPA
Medical Director – Sonic Genetics Laboratory
As a pathologist, Karl supervises testing for immunodeficiency, allergic and autoimmune diseases, as well as our expanding menu of genetic testing, including DNA relationship testing, esoteric immune disease genetic tests and pharmacogenomic testing.

DR SCOTT MEAD  MSc (Hons), PhD, MBChB, BHB, FRCPA
Genetic Pathologist
Dr Scott Mead graduated from the University of Auckland (New Zealand) where he also gained a PhD in Molecular Medicine. His pathology training was undertaken at Christchurch School of Medicine (University of Otago) and Royal Prince Alfred Hospital, Sydney. Dr Mead has a long-standing interest in cancer genetics and is currently researching the clinical application of personal cancer genome sequencing at the Kinghorn Cancer Centre (Garvan Institute). He is also involved in targeted oncology testing at SydPath Pathology (St Vincent’s Hospital). Dr Mead is currently a Conjoint Senior Lecturer at the School of Medical Sciences, University of NSW.