Pharmacogenomics

What is Pharmacogenomics?

Pharmacogenomics can be thought of as a combination of pharmacology and genomics. It is the science of how an individual's genetic makeup can influence the way they metabolize drugs; and therefore, how long a drug stays effective in their system. A person's genetic makeup not only determines eye and hair color and disease susceptibilities, it also predicts how an individual will respond to drugs based on their genetic variability. Understanding this, and using Pharmacogenomics information as part of a prescribing decision, can help achieve a more personalized solution for patients.

How Does the Testing Work?

Medical Diagnostic Laboratories (MDL) offers a broad menu of Pharmacogenomics testing using state-of-the-art Next Generation Sequencing (NGS) technology. From a patient's blood or saliva specimen, germline DNA is extracted for testing. This extracted germline DNA is used to prepare a library of short fragments that represent the genes of interest. This allows the patient's DNA sequence to be read many times over, sometimes referred to as deep sequencing, so that we can detect, with a very high degree of confidence, all of the heritable DNA variants present. Finding these variants, and determining how they modify the function of the protein encoded in that gene, is the basis of Pharmacogenomics.

What Genes are Included in Testing?

Pharmacogenomics testing offered by MDL examines forty genes (**Table 1**) and interrogates a total of 138 individual loci. Most are Single Nucleotide Variant (SNV) loci, but there are some single-base and triple-base insertion/deletion (indel) variants as well. The coverage can be simply one or two key SNVs per gene, for example in the Solute-Carrier Organic Carrier Anion Transporter Family Member 1B1 (SLOC1B1) gene, where variants may determine myotoxicity as a side effect of simvastatin use, to twenty-one loci in the cytochrome P450 gene, CYP2D6 whose action modifies the efficacy of many drugs in several disease classes.

Table 1: Genes found in the MDL Pharmacogenomics Solutions test panel. A whole blood or saliva specimen is required for testing.

ABCB1	CYP2C9	GABRA6	OPRM1
ABCG2	CYP2D6	GABRP	SLCO1B1
ADRA2A	CYP3A4	GRIK4	TPMT
ANKK1	CYP3A5	HTR2A	UGT1A1
APOE	DBH	HTR2C	UGT2B15
COMT	DPYD	ITGB3	UGT2B7
CYP1A2	DRD1	KIF6	VKORC1
CYP2B6	DRD4	MTHFR	HLA-A*3101
CYP2C19	F2	OPRD1	HLA-B*1502
CYP2C8	F5	OPRK1	HLA-B*5701

What Conditions Can Be Tested?

Pharmacogenomics testing offered by MDL provides information about genetic influences on the dosing, toxicities, and efficacy of 197 commonly-prescribed drugs, divided into seven broad subgroups: (i) Cardiology, (ii) Immunology, (iii) Infectious Disease, (iv) Malignant Disease, (v) Pain Management, (vi) Psychiatric Disorders, and (vii) Other. These tests can be ordered for individual drugs such as citalopram, atorvastatin, fluorouracil or prednisolone among others, or for whole classes of drugs such as Beta-Blockers, anti-HIV drugs, antiepileptics or anti-inflammatories.

What Potential Clinical Problems Can Be Avoided and What Advantages Can Be Gained?

Pharmacogenomics testing can offer assistance in determining the choice of drug to avoid adverse effects as well as the choice of dose, to obtain optimal, patient-personalized, benefit. Some illustrative examples are shown below:

Cardiology: Drugs included cover the broad categories of statins, antiplatelet agents, calcium-channel blockers and beta-blockers, and also take into account thrombophilia. Reports include the activity of sixteen genes* affecting the function of thirty-five drugs*, as well as the actions of two serum proteins, Factor-V and Factor-II.

- **STATINS**: Statins, such as atorvastatin, are metabolized by nine main genes including ABCB1, ABCG2, APOE, CYP2C9, CYP2D6, CYP3A4, CYP3A5, KIF6, and SLCO1B1. Issues arise for patients when they have one or more "fast metabolizer" variant alleles in one or more of these genes. This results in lower plasma concentrations per unit dose, meaning lower than expected response to treatment, for example in rebalancing LDL and HDL cholesterol. In some cases, this may increase a patient's risk for myocardial infarction relative to "regular" metabolizers or patients in general. Patients may also be genetically-susceptible to greater than expected risk of myalgia and muscle damage.

- **ANTIPLATELET AGENTS**: Metabolism of antiplatelet agents is regulated by ten main genes including ABCB1, CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, ITGB3 and SLCO1B1. Many antiplatelet agents such as clopidogrel, are "prodrugs" meaning they need to be effectively metabolized in order to become fully active. Understanding that a patient does not metabolize a drug well may allow one to consider the use of an alternative, directly active drug, such as ticagrelor. However, some patients may be contraindicated for ticagrelor, because they fail to metabolize it and so develop higher serum concen-

trations, resulting in an increased bleeding risk. Interestingly, benefit from the commonly-prescribed aspirin may also vary genetically, and we report that, too.

- **WARFARIN RELATED DRUGS**: Warfarin, referring specifically to Coumadin and related compounds, is a commonly-prescribed anticoagulant. While very effective and inexpensive, it has a narrow effective dose-window that is compromised by a wide intra-individual metabolic rate, making appropriate dosing challenging. Metabolism of warfarin is controlled by two enzyme systems: the CYP2C9 member of the cytochrome P450 family and the Vitamin K-Epoxide Reductase Complex, VKORC1. For this reason, the FDA recommends to dose warfarin according to genotypes of CYP2C9 and VKORC1, as shown in **Table 2**. CYP2C9 alone has over 30 heritable variant alleles, of differing enzymatic activity. These variant alleles often have low metabolic degradation of warfarin, leading to accumulation and high bleeding risk, thereby necessitating a reduced dose. Similarly, heritable variants of VKORC1 may also permit warfarin accumulation and additional bleeding risk. Therefore, it is necessary to combine CYP2C9 and VKORC1 genotypes to determine an appropriate dose.

Table 2. 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 (FDA). Reproduced from updated warfarin (Coumadin) product label.

VKORC1 Genotype (-1639G>A, rs9923231)	CYP2C9 *1/*1	CYP2C9 *1/*2	CYP2C9 *1/*3	CYP2C9 *2/*2	CYP2C9 *2/*3	CYP2C9 *3/*3
GG	5-7	5-7	3-4	3-4	3-4	0.5-2
GA	5-7	3-4	3-4	3-4	0.5-2	0.5-2
AA	3-4	3-4	0.5-2	0.5-2	0.5-2	0.5-2

- **CALCIUM-CHANNEL BLOCKERS**: Metabolism of drugs such as amlodipine and nifedipine is regulated by the genes CYP3A4 and CYP3A5. They are often used to help maintain a safe arterial pressure in a diagnosis of hypertension, when other drugs may fail to do so. Genetic testing can help predict how such patients may benefit from this class of drugs.

- **BETA-BLOCKERS**: Metabolism of beta-blockers is regulated by three main genes including ABCB1, CYP2D6, and UGT1A1. These drugs, for example metoprolol, are used to maintain a steady heart-rate, protect from second heart attacks, and treat hypertension. Certain patients may metabolize these drugs more quickly than others, resulting in a failure to maintain an adequate serum concentration. Genetic testing can therefore help guide dosing as well as alternative drug decisions.

- **THROMBOPHILIA**: Development of blood clots, also known as thrombi, usually in the deep veins of the legs or in the fine veins of the lungs, is known as Thrombophilia. Two serum proteins, Factor-V and Factor-II, promote the clotting cascade. Variation in their genes (F2 20210G>A and F5 Leiden) can produce proteins that are much more aggressive in promoting clotting than those in the majority of the population.

Identifying these patients through genetic testing, may help with the decision making regarding which anticlotting drugs to prescribe.

- **CONGESTIVE HEART FAILURE**: When the ability of the heart to move blood around the body becomes diminished to the point that the patient begins to accumulate fluid, the patient is said to have Congestive Heart Failure (CHF). This condition is commonly treated with digoxin. The ability to respond correctly to digoxin is regulated by the gene ABCB1. Certain patients may metabolize digoxin more quickly than others, resulting in a failure to maintain an adequate serum concentration. Genetic testing can determine how the patient metabolizes digoxin in order to help guide dosing.

- **ANTIARRYTHMATICS:** Abnormal heart rhythm, also known as arrhythmia, can be short term or prolonged, requiring treatment with drugs such as flecainide or propafenone. The ability to respond to these agents is regulated by the cytochrome P450 gene, CYP2D6. The complex consequences of a patient's CYP2D6 type can only be determined by Pharmacogenomic testing, which can help guide dosing or drug choice changes.

- **ANTIHYERTENSIVES**: Drugs for the general treatment of high blood pressure can fall into several groups such as: sodium-channel blockers (e.g., sparteine), angiotensin- II receptor antagonists (e.g., olmesartan), or adrenergic antagonists (e.g., debrisoquine). Metabolism of such drugs can often be slower than normal, according to the genotype of five key genes including ABCB1, CYP2D6, CYP2C9, MTHFR and SLCO1B1. This may require a lower dose or the choice of a therapeutic alternative.

Pain Management Using Opioids and Sedatives: Opioids remain the drug of choice for relief of temporary, but severe, pain. These drugs generally, and certain ones in particular such as codeine, fentanyl, hydrocodone, methadone, morphine, oxycodone and tramadol, have their benefits and side-effects which are affected by patient genotype, making pharmacogenomics analysis important in effective prescribing. We report the function of eight genes, affecting the function of ten specific drugs and opioids as a class. Sedation is used in a variety of clinical settings, including terminal cancer care. It is important to choose and dose drugs appropriately. An examination of CYP2B6, CYP2C19, CYP2D6, CYP3A4, CYP3A5 and SLCO1B1 will assist in prescribing five common sedatives.

- **RISK OF DEPENDENCY:** There is always a risk to develop dependency with opioids in general. This phenomenon is associated with alleles in ABCB1, ANKK1, COMT, CYP2B6, CYP2C19, CYP3A4, DBH, DRD1, MTHFR, OPRD1 and OPRM1.

- **RESPIRATORY OR CENTRAL NERVOUS SYSTEM DEPRESSION**: Certain opioids, such as codeine and hydrocodone, can confer respiratory or central nervous system (CNS) depression. In nursing mothers, this may be transferred to the infant via breast milk. Where this is a concern, the ABCB1 and OPRM1 genes should be examined.

- **REDUCED EFFICACY**: Most commonly, allelic variants can alter the rate at which these drugs are metabolized, leading to reduced efficacy per unit dose. Opioids generally, and certain ones in particular such as codeine, fentanyl, hydrocodone, methadone, morphine, oxycodone and

tramadol, are regulated by ABCB1, COMT, CYP2B6, CYP2D6, CYP3A4, DBH, OPRD1 and OPRM1, requiring alternative dosing to be considered.

Psychiatric Disorders: Conditions such as depressive disorder, anxiety, and schizophrenia are long-term chronic problems where prescribing is notoriously difficult. Furthermore, there are well-recognized problems in changing a patient's medication in these conditions. We report on the function of twenty-four genes affecting the function of sixty-two drugs, including Selective Serotonin Reuptake Inhibitors (SSRIs) as a general class.

- **DEPRESSIVE AND MAJOR DEPRESSIVE DISORDER:** This is a serious and debilitating disorder characterized by persistent and pervasive feelings of sadness and worthlessness that interfere with normal life. The cause is unknown and the diagnosis is by history rather than physiological testing. Consequently, therapeutic approaches have been varied and often, empirical. Pharmacogenomic analysis of ABCB1, ADRA2A, ANKK1, COMT, CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A5, DRD4, GABRA6, GABRP, GRIK4, HTR2A, HTR2C and MTHFR can help determine the necessary dose and/ or likely efficacy of many commonly-used drugs, including modern SSRIs such as citalopram.

- **AGITATION AND ANXIETY:** While related to depressive disorder and also treated with SSRIs, this condition and its related insomnia are considered distinct and are also treated with benzodiazepines (e.g., lorazepam), serotonin-norepinephrine reuptake inhibitors (e.g., venlafaxine), or general sedatives (e.g., midazolam). A consideration of the allelic nature of ADRA2A, COMT, CYP1A2, CYP2C19, CYP2D6, CYP3A4, CYP3A5, GABRA6, GABRP, HTR2A, and UGT1B15 may guide dosing and drug selection.

- **SCHIZOPHRENIA:** In this serious, chronic, and debilitating condition, patients may appear to have lost touch with reality. They may display a range of symptoms that set them apart, including the inability to reason, focus, process, and work with information, relate to others, and having delusions and hallucinations. The cause is unknown and treatment is symptom-related and, as in the case of depression, often empirical. There is a broad range of antipsychotic class drugs such as clozapine, risperidone, and trifluoperazine, whose metabolism is defined by CYP2D6, with consequent dosing changes. Interestingly, important side effects including weight-gain and hormonal disruption, such as prolactin in female patients, are regulated by ANKK1, COMT, CYP1A2, HTR2A and MTHFR. Pharmacogenomics testing offered by MDL adds ABCB1, CYP2C9, CYP3A4, CYP3A5, DRD1, GRIK4 and HTR2C to provide a picture that is advisory for thirteen drugs overall for this condition.

- **OTHER CONDITIONS:** Addiction, Attention Deficit and Hyperactivity Disorder (ADHD), Autism spectrum disorder, and Epilepsy can also show drug responses and toxicities that may be modified pharmacogenomically.

Malignant Disease: While malignancies can arise in almost any tissue, the major epithelial tumors of the breast, ovary, colon, and lung continue to comprise a majority of long- term post-surgical treatments. Several broad classes of drugs exist, and many of these have effects that are modified pharmacogenomically.

Pharmacogenomics testing offered by MDL uses fourteen genes to address thirty-five common anticancer drugs and three antiemetics.

- **STEROID HORMONE INHIBITORS**: Most commonly prescribed for breast cancer, these drugs work by antagonizing the growth promoting effects of estradiol on the patient's tumor cells. While tamoxifen is frequently used, enhanced metabolism can reduce the effective titer of this and similar drugs, potentially reducing the beneficial effect. A consideration of the ABCB1, CYP2B6, CYP2C19, CYP2D6 and CYP3A4 genes can provide valuable information.

- **MODERN ENZYME INHIBITORS**: Kinase and topoisomerase inhibitors such as irinotecan, gefitinib, and sunitinib, have recently become available for prescription in ovarian, breast, colorectal, and lung cancers, as well as for other tumor types. The various genetic forms of ABCB1, ABCG2, CYP2B6, CYP3A5 and SLCO1B1 regulate the metabolism of these relatively new drug types.

- **PLATINUM-CONTAINING DRUGS**: The three common platinum derivatives, collectively referred to as the platins including carboplatin, cisplatin, and oxaliplatin, are primarily prescribed for ovarian cancer and have been for a considerable time. More recently, they have been shown to be effective in cases of colon, endometrial, and lung cancer, as well as testicular cancer in men. When prescribed alone, the genes ABCB1, ABCG2, CYP2C19, CYP3A5, MTHFR and TPMT should be examined as guides to efficacy variation. However, they are often given in combination with other drugs such as paclitaxel or fluorouracil, as described below. In these cases, the genes CYP3A4 and SLCO1B1, or DPYD and SLCO1B1, should be added, respectively.

- **ALKALOIDS**: These plant-derived drugs have proven to be powerful anticancer tools. Commonly-prescribed for breast, ovarian, or lung cancer, and often in combination with other drug classes, they continue to be effective several decades after having first been introduced. Drugs such as paclitaxel, docetaxel, and vincristine, will vary in their efficacy according to the patient's genetic makeup of ABCB1, CYP3A4, CYP3A5 and SLCO1B1.

- **MORE TRADITIONAL ANTINEOPLASTICS**: Despite the recent introduction of a range of treatments, there remains a strong and core role for standard treatments such as capecitabine, cyclophosphamide, doxorubicine, fluorouracil, and methotrexate, across a spectrum of solid and hematological malignancies. Often these may be used in combination with more advanced treatments, such as carboplatin. Genetic variation in ABCB1, ABCG2, CYP2B6, CYP2C9, CYP2C19, CYP3A4, CYP3A5, DYPD, MTHFR and SLCO1B1 can all influence the efficacy of these drugs.

Immunology and Inflammatory Disease: Chronic inflammatory disorders and autoimmune diseases are widespread and debilitating, but mechanistically distinct, requiring careful drug choice and dosing.

Pharmacogenomics testing offered by MDL encompasses nine of the most commonly prescribed drugs in this clinical

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area and takes into account eight genes. In transplant recipients being maintained on antirejection regimens, you can monitor the effect of eight common treatments using seven genes.

- **AUTOIMMUNE AND CHRONIC INFLAMMATORY DISEASE:** The mechanistic nature of these disorders varies markedly by anatomic site, as does the treatment. Conditions such as rheumatoid arthritis, systemic lupus erythematosus, gout, and inflammatory bowel disease are widely treated with an array of drugs whose function can be anti-inflammatory, for example celecoxib and cytotoxic (cyclophosphamide or methotrexate). One can gain important insight into individualizing your patient's experience with such drugs by using information for genetic analysis of ABCB1, ABCG2, CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP3A4, MTHFR and/or SLCO1B1.

- **TRANSPLANTATION**: Preventing graft rejection is both similar and distinct to the problem of halting autoimmune attack. Current drug regimens are often considered to be lifetime administrations and so understanding the best solution for a given patient is of paramount importance. By analyzing the genes ABCB1, CYP2B6, CYP2C9, CYP2C19, CYP3A4, CYP3A5, MTHFR and SLCO1B1, one can help ensure the use of the best drugs from a broad panel that ranges from cyclosporine and tarcolimus to cyclophosphamide and prednisone.

- **HIV/AIDS:** Treatment of HIV/AIDS has been revolutionized by the introduction of advanced antiviral drugs, used both singly and in combination cocktails. A broad range of efficacies, toxicities, and survival benefits has been experienced and reported, in this field that continues to rapidly develop. Due to the fact that providing the best, most personalized care is a high priority in this patient population, a pre- prescribing examination of ten drug-metabolizing genes may be of great benefit. ABCB1, APOE, CYP2B6, CYP2C19, CYP2D6, CYP3A4, CYP3A5, HTR2A, and UGT1A1 will provide information that will help with prescribing decisions

Other Conditions: The importance of pharmacogenomics continues to expand into other areas. For example, prescription choice for long-term administration of oral contraceptives may be modified by genetic variants of the blood clotting system, such as FACTOR 2.

How is Testing Ordered?

It is important that physicians are clear about the medical benefit patients will gain from personalized treatment with the assistance of Pharmacogenomic data. Once the medical benefit has been determined with a statement of medical need, testing can be ordered in one of three ways:

- **By Condition:** As an example, if treating a patient for Depressive Disorder or Major Depressive Disorder, with or without Anxiety, simply select the appropriate boxes in the **Psychiatric Disorders** section on the front of MDL's Pharmacogenomics Test Requisition Form. Result reports will include data for all drugs listed in the panels ordered.

- **By Drug:** When drug choice is already determined by medical and/or insurance coverage reasons, such as in the example of a generic statin, a drug- specific test may be selected on the back of MDL's Pharmacogenomics Test Requisition Form. You may select more than one drug, in more than one class (for example, an opiate analgesic and an antidepressant).

- **By Gene:** If there is a specific gene of interest as listed in Table 2 of this bulletin, simply write in the specific gene(s) in the section **Other Tests/Panels** located in the bottom right corner of the front page of MDL's Pharmacogenomics Test Requisition Form.

How Long Will Testing Take?

Turnaround time for Pharmacogenomics testing offered by MDL is approximately 10 to 14 business days.

Pharmacogenomic Testing Limitations

Pharmacogenomics testing offered by MDL is provided to aid prescribing decisions by physicians. It is neither intended to be, nor provided as, medical advice. The responsibility for decisions regarding prescribing and all other aspects of a patient's clinical management lies with the ordering physician or other authorized healthcare professionals, taking into account Pharmacogenomic data in the context of all other aspects of the individual patient's circumstances.

Although a patient's genetic makeup is an important part of how they will metabolize or otherwise respond to particular drugs, it is only one part, as responses to drugs may be influenced by a number of things including dietary and other consumption habits, for example.

The information provided in Pharmacogenomics testing result reports offered by MDL is believed to be current at the date the report is issued, based upon research published in the scientific and clinical peer-reviewed literature. References to this literature can be provided upon request. However, the report and its contents are provided and accepted "as is" and without warranties of any kind, on the clear understanding that scientific opinions can and do change and this may be reflected in reports issued by MDL over a period of time.

Patients and physicians may wish to consult a Genetic Counselor to help interpret results to provide the greatest benefit to patients. MDL does not offer Genetic Counseling services and any cost of such services is not included in the cost of the Pharmacogenomics testing offered by MDL.

Pharmacogenomics testing offered by MDL is provided for clinical use, and not as an investigational or research tool. It should be noted that DNA testing is never a substitute for best-practice clinical monitoring.

MDL has introduced the Pharmacogenomics App which looks at commonly-prescribed drugs in fields such as cardiology, anti-depressants, pain management, malignant disease and others, and indicates whether genetic variants might modify the optimal course of therapy for individual patients. MDL's Pharmacogenomics App is now available for free download for Apple devices from the iTunes App Store or for Android devices from the Google Play Store, **http://www.mdlab.com/resources/app/**