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The Laboratorian SM

Pharmacogenomics:

What is it, and how should you use it?

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In this era of personalized medicine, physicians and medical providers are constantly searching for tools that enable them to tailor their medical care better to each individual patient. Patients are looking for this approach from their providers for themselves and their families as well. There isn't much that's more personal to an individual than their genome. The most frequent outcome of a patient/physician encounter involves the writing of a prescription. Pharmacogenomics is a way to combine these two things, a way to personalize prescribing to each individual patient's genetics.

What is Pharmacogenomics?

The term "Pharmacogenomics" is often used interchangeably with "Pharmacogenetics". While "pharmacogenetics" refers to only one gene, in "pharmacogenomics" we can consider the effect of the patient's overall genetic environment.

Pharmacogenomics provides physicians with a means to determine whether the patient's genetics will modify the rate at which they will metabolize drugs. This information allows the physician to decide whether the standard dose is appropriate. The physician may choose to prescribe the drug at a different starting dose or to prescribe a different drug entirely. Pharmacogenomics can reveal the likelihood of adverse effects and drug-drug interactions. It can also provide insight into poor responses to one drug that may occur due to the patient's inappropriate metabolism of another being given in parallel.

Although the majority of patients will respond predictably to the standard dose and regimen of most drugs, some patients do not. An unexpected response may lead to a drug being ineffective (e.g. Plavix) or hyper-effective (e.g. warfarin), and this may be potentially very dangerous for the patient. Pharmacogenomic testing takes much of the risk out of the picture, allowing the use of an individual's genetic data to help physicians tailor their prescribing to an individual patient.

Pharmacogenomic testing provides a means for physicians to consider which medications may be appropriate for a particular patient before ever actually writing a prescription. It also allows physicians to consider alternate medications more effectively in a situation where the patient is not responding as expected to a particular medication. As illustrated in **Figure 1**, Pharmacogenomic testing is a way to look at a group of patients with the same diagnosis and determine who amongst them will respond to a given drug as expected, and who will not.

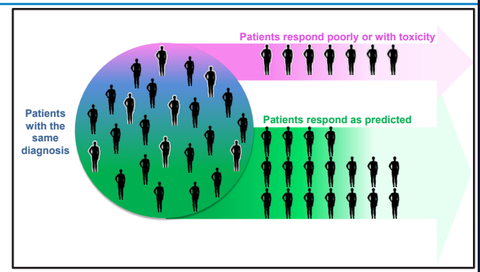


Figure 1. Pharmacogenomics testing - contrasting patients who respond to a drug as expected and those that do not.

How Well Does it Work?

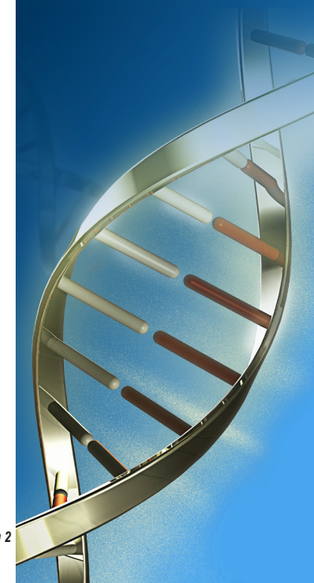
As is often the case with cutting-edge techniques, the initial studies of the utility of pharmacogenomics (PGx) testing have fallen on both sides of the aisle, but a pattern is emerging of strong clinical utility, particularly in the field of antidepressant prescribing in family medicine and obstetrics. Mostly, this has come from the results of randomized studies with relatively large numbers of patients.

In 2017, Perez et al conducted a randomized, double-blind controlled trial of 316 patients requiring antidepressants. The Pharmacogenomics-guided group had a higher 12-week responder rate (p=0.014) and this beneficial effect was even higher, when patients had already experienced at least one treatment failure (1). This expanded upon previous studies; Winner et al, again using a randomized double-blind study design, showed that 36% of the PGx-guided group responded to treatment, while only 20% of the control group did (OR = 2.14). Interestingly, outright remission was also higher in the PGx-guided group (OR = 2.75) (2). Further, Hall-Flavin et al used randomized patients once again, and demonstrated that the PGx-guided group showed greater improvement of clinical scores (p<0.0001). Most interestingly, patients prescribed a medicine that was later shown to be most incompatible with their PGx profile, showed least improvement (p<0.007) (3).

The question of cost-effectiveness of PGx guidance has also been addressed and shown to be positive. In 2017, Colson et al studied 243 randomized patients for PGx-guided therapy, and reported almost half the rate of adverse effects in the PGx-guided group (28% vrs 53%, p<0.001). Furthermore, they showed that the cost of managing those adverse drug effects (ADEs) that did

Continued.....pg 2

WHAT'S INSIDE



WINTER 2017 | VOLUME 10 No. 1 | Yearly Publication P6 New Tests in 2017 P5 Recent Publications P4 Q&A Section, & Journal Watch

The Laboratorian SM

Continued From.....pg 1

occur in the PGx group was 84% lower than treating ADEs in the control group (p = 0.019) (4). An additional study by Hornberger et al showed that PGx-guided treatment improved the response rate by 70% (OR = 1.7), relative to control. They were also able to predict that patients in the PGx-guided group would have healthcare cost savings of $3,711, and work productivity cost savings of $2,553 (5).

Thus, while disagreement always exists in the clinical scientific literature, the body of evidence is clearly showing the utility of pharmacogenomics-guided treatment, in terms of overall efficacy, and lower health-care costs to patients.

The Example of Warfarin

Warfarin (as "Coumadin" and related compounds), is a commonly-prescribed anti-coagulant. While very effective and inexpensive, it has a narrow effective dose-window that is compromised by a wide intra-individual metabolic rate which can make appropriate dosing a challenge.

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 Food and Drug Administration (FDA) recommends dosing warfarin according to the genotypes of CYP2C9 and VKORC1, as shown in **Table 1**. 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, which necessitate 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 1. Recommended daily warfarin doses (mg/day) to achieve a therapeutic INR based on CYP2C9 and VKORC1 gentoype using the warfarin product insert approved by the United States Food and Drug Administration (FDA). Adapted from Table 1 od the 2011 guideline manuscript. Reproduced from updated warfarin (Coumadin) product label.

VKORC1 Genotype (-1639G>A, rs9923231)	CYP2C9*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

It's About Drugs and Prescribing

The purpose of any dosing regimen is to first reach an active level and then to keep the drug at, or close to, that level for the course of administration. Understanding the impact of genetic variation in drug metabolism is really about understanding how this variation modifies the steady-state levels of the drug in plasma. This in turn is achieved by balancing ingestion against excretion. Usually it is appropriate to think of drug metabolism as being associated with loss of the active drug. However, drugs come in two basic forms: "Drugs", where the compound ingested is actually chemically active, and "Prodrugs", where the compound ingested is inert and has to be metabolized to achieve its active form. The rate at which the ingested compound is metabolized will be opposite in these cases.

For immediately active compounds (drugs) the relationship between metabolic rate and serum titer is straightforward. If the patient ingests a standard dose and metabolizes it more rapidly than expected, the time for which s/he will maintain a required level will be less than expected. Therefore, the necessary therapeutic benefit may not be realized. Conversely, if the patient is a "slow" metabolizer, the drug may slowly but surely increase its titer, perhaps reaching unsafely high levels.

For Prodrugs, the effect is the opposite. Slow metabolizers may fail to ever reach active titers. Meanwhile, rapid metabolizers may spike into higher-than-expected levels and then fall below the required active titer for a period of time before the next dose is taken (**Figure 2**).

The Importance of Prodrugs

Prodrugs are common. Examples in three fields (malignant disease, platelet inhibition, and pain management) can illustrate this:

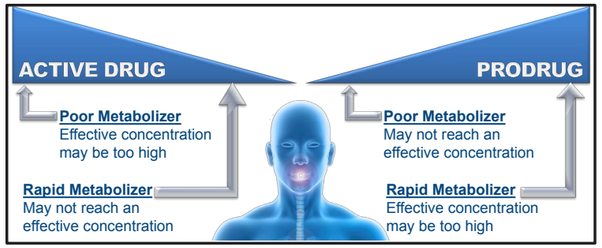


Figure 2. The relationship between metabolic rate and serum titer in active drugs versus prodrugs.

Tamoxifen is an anti-estrogen commonly used in the prophylaxis of post-surgical breast cancer if the primary tumor is estrogen-receptor (ER) positive. Although, it is only one of a number of anti-estrogens available for this purpose, it is by far the most widely used. Tamoxifen, the chemical, is therapeutically inactive and must be metabolized to afimoxifene by the enzyme CYP2D6 in order to mediate its therapeutic effect. Individuals vary genetically as to their rate of function of CYP2D6, from "Ultrarapid" CYP2D6 metabolizers, through "Normal" and "Intermediate", to people who have no CYP2D6 activity at all. It is interesting to consider whether understanding the CYP2D6 genotype of a cancer patient might better inform the choice of anti-estrogen under circumstances where that class of drugs was deemed appropriate (**Figure 3**).

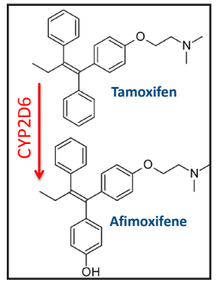


Figure 3. Chemical structure of Tamoxifen and its therapeutically active metabolite afimoxifene.

Plavix, as it's generic form Clopidogrel, is the most-commonly prescribed platelet inhibitor given almost universally to patients who have received a cardiac stent following a blockage of the heart's blood supply. Like Tamoxifen, the chemical entity Clopidogrel is therapeutically inactive because it was designed for good gastrointestinal uptake. In the liver, it is hydroxylated by CYP2C19 to its active form, which inhibits platelet adherence. However, like CYP2D6, CYP2C19 has multiple genetic forms that range in activity from Ultrarapid to Inactive. If activity is reduced or absent, the appropriate therapeutic dose may not be delivered regardless of the ingested dose. Low-functioning variants are associated with increased reclotting and mortality rates, with many second clots forming in the stent itself. Alternative anti-platelet agents (such as Ticagrelor) are available for patients who have genetically low CYP2C19 activity (**Figure 4**).

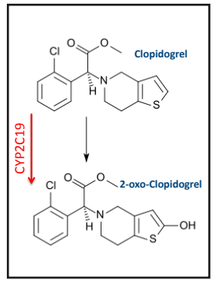


Figure 4. Chemical structure of clopidogrel and its therapeutically active metabolite 2-oxo-clopidogrel.

Codeine, and a number of its derivatives, are analgesic and antitussive agents, based on morphine. While codeine does have a small amount of activity in its own right, morphine has a greater affinity for the mu-opioid receptor OPRM1 and hence greater and more sustained effect. Once again, there is significant input from CYP2D6 in the metabolism of codeine to morphine. While normal metabolizers may get efficient pain relief, faster metabolizers may have a larger than expected dose of morphine delivered in a short space of time. Conversely, low metabolizers, or individuals whose CYP2D6 is inactive, may not experience the relief expected. Since codeine and morphine are mobilized in breast milk, infants of nursing mothers whose CYP2D6 activity is altered may suffer respiratory suppression, and in fact the FDA has issued a specific warning about this (6) (**Figure 5**).

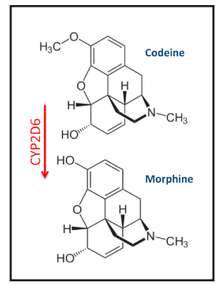


Figure 5. Chemical structure of codeine and it's therapeutically active metabolite morphine.

Continued.....pg 3

Pharmacogenomics Testing - Whole Blood (ACD Solution A) - MALIGNANT DISEASE

3301	**Ikaloids** – Vincristine (ABCB1)
3302	**Alkylating Agents**-Cyclophosphamide, Dacacarbazine (CYP1A2, CYP2B6, CYP2C19, CYP3A4, MTHFR, SLCO1B1)
3303	**Antimetabolites** - Cytarabine, Fludarabine, Mercaptopurine, Methotrexate, Silibinin (ABCB1, MTHFR, SLCO1B1, TPMT)
3304	**Anthracyclines**-Anthracyclines (gen), Doxorubicin, Epirubicin, Idarubicin (ABCB1, CYP2B6, CYP2C19, SLCO1B1)
3305	**Kinase Inhibitors** - Gefitinib, Icotinib, Imatinib, Sorafenib, Sunitinib (ABCB1, ABCG2, CYP2B6, CYP2D6, CYP3A5, SLCO1B1)
3306	**Platinum Derivatives** - Carboplatin, Cisplatin, Oxaliplatin, Platinum Compounds (gen) (ABCB1, ABCG2, CYP2C19, CYP3A5, MTHFR, TPMT)
3307	**Steroid Hormone Inhibitors** - Mitotane, Tamoxifen (ABCB1, CYP2B6, CYP2C19, CYP2D6, CYP3A4)
3308	**Taxanes** - Docetaxel, Paclitaxel, Taxanes (gen) (ABCB1, CYP3A4, CYP3A5, SLCO1B1)
3309	**Topoisomerase Inhibitors** - Etoposide, Irinotecan (ABCB1, SLOC1B1, UGT1A1)
3310	**Uracil Derivatives** - Capecitabine, Fluorouracil, Folfox, Folox, Leucovorin, Tegafur, Xelox (ABCB1, ABCG2, DYPD, MTHFR, SLCO1B1)
3311	**Antiemetics** - Dolasetron, Granisetron, Ondansetron (ABCB1, CYP2C9, CYP2D6,CYP3A5)

PSYCHIATRIC DISORDERS (INCLUDING ADDICTION)

3401	**Addiction to Alcohol, Cocaine, Heroin, Opioids, Tobacco** - Bupropion, Disulfiram, Levodopa, Methadone, Naloxone, Naltrexone, Nicotine (ABCB1, ANKK1, COMT, CYP2B6, CYP2C19, CYP3A4, DBH, DRD1, MTHFR, OPRD1, OPRM1)
3402	**ADHD**-Atomoxetine, Dextroamphetamine, Methylphenidate (ADRA2A, CYP2D6, DRD1)
3403	**Alzheimer's Disease** - Donepezil, Galantamine, Olanzapine, Risperidone (ABCB1, ANKK1, CYP1A2, CYP2C9, CYP2D6, CYP3A5, HTR2A, MTHFR)
3404	**Anxiety, Insomnia, Severe Agitation**-Dexmedetomidine, Escitalopram, Lorazepam, Midazolam, Oxazepam, Venlafaxine (ADRA2A, COMT, CYP1A2, CYP2C19, CYP2D6, CYP3A4, CYP3A5, GABRA6, GABRP, HTR2A, UGT2B15)
3405	**Autism Spectrum Disorders** - Quetiapine, Risperidone (ABCB1, ANKK1, COMT, CYP2D6, CYP3A4, CYP3A5, HTR2A)
3406	**Bipolar Disorder** - Lithium, Olanzapine, Quetiapine (ABCB1, ANKK1, CYP1A2, CYP2C9, CYP2D6, CYP3A5, COMT, DRD1, HTR2A, MTHFR)
3407	**Depressive Disorder and Major Depressive Disorder**-Agomelatine, Amitriptyline, Antipsychotics (gen), Citalopram, Clomipramine, Desipramine, Diazepam, Doxepin, Escitalopram, Fluoxitine, Fluvoxamine, Imipramine, Maprotiline, Milnacipran, Mirtazapine, Nortriptyline, Olanzapine,Opipramol, Paroxetine, Quetiapine, Sertraline, SSRIs (gen), Trimipramine, Venlafaxine, Vortioxetine (ABCB1, ADRA2A, ANKK1, COMT, CYP1A2, CYP2B6, CYP2C19, CYP2C9, CYP2D6, CYP3A5, DRD4, GABRA6, GABRP, GRIK4, HTR2A, HTR2C, MTHFR)
3408	**Epilepsy** - Antiepileptics (gen), Carbamazepine, Clobazam, Lamotrigine, Mephenytoin, Phenobarbital, Phenytoin, Valproic acid (ABCB1, ABCG2, ANKK1, CYP1A2, CYP2C19, CYP2C9, CYP3A4, CYP3A5, UGT2B7)
3409	**Parkinson's Disease** - Entacaptone (COMT)
3410	**Schizophrenia** - Antipsychotics (gen), Aripiprazole, Chlorpromazine, Clozapine, Fluphenazine, Haloperidol, Iloperidone, Nemonapride, Olanzapine, Quetiapine, Risperidone, Thioridazine, Trifluoperazine, Zuclopenthixol (ABCB1, ANKK1, COMT, CYP1A2, CYP2C9, CYP2D6, CYP3A4, CYP3A5, DRD1, GRIK4, HTR2A, HTR2C, MTHFR)

INFECTIOUS DISEASE

3501	**HIV/AIDS**-Atazanavir, Efavirenz, Etravirine, Indinavir, Lamivudine, Lopinavir, Nelfinavir, Nevirapine, Ritonavir, Zidovudine (ABCB1, APOE, CYP2B6, CYP2C19, CYP2D6, CYP3A4, CYP3A5, UGT1A1)
3502	**Antifungals and Antibiotics** - Daptomycin, Dicloxacillin, Erythromycin, Rifampicin, Sulfonamides (gen), Voriconazole (ABCB1, CYP2C9, CYP2C19, CYP3A4, SLCO1B1)

IMMUNOLOGY / IMMUNE MODULATION

3601	**Transplantation** - Busulfan, Cyclophosphamide, Cyclosporine, Everolimus, Methylprednisone, Prednisone/Prednisolone, Sirolimus, Tacrolimus (ABCB1, CYP2B6, CYP2C19, CYP2C9, CYP3A4, CYP3A5, MTHFR, SLCO1B1)
3602	**Rheumatoid Arthritis** - Leflunomide, Methotrexate, Sulfasalazine (ABCB1, ABCG2, CYP1A2, MTHFR, SLCO1B1)
3603	**Type-II Diabetes** - Repaglinide, Sulfoureas (gen), Urea Derivatives (gen) (CYP2C8, CYP2C9, SLCO1B1)
3604	**Gastritis and Colitis** - Esomeprazole, Lansoprazole, Omeprazole, Pantoprazole, Rabeprazole, Tacrolimus (ABCB1, CYP2C19, CYP3A4, CYP3A5)
3605	**nflammation** - Celecoxib, Dexamethasone, Diclofenac, Flurbiprofen, Lornoxicam, Prednisone/Prednisolone (ABCB1, CYP2C9)
3606	**Systemic Lupus Erythematosus**-Cyclophosphamide (CYP2B6, CYP2C19, CYP3A4, MTHFR, SLCO1B1)
3607	**Gout** - Allopurinol (ABCG2)
3608	**Antihistamines** - Fexofenadine (ABCB1)
3609	**Antiasthmatics** - Zafirlukast (CYP2C9)

OTHER

3701	**Anaesthesiology** - Nitrous Oxide (MTHFR)
3702	**Beta Thalassemia** - Deferasirox (CYP1A2, UGT1A1)
3703	**Narcolepsy** - Modafinil (ABCB1)
3704	**Contraception** - Oral Contraceptives (gen) (F2, F5)
3705	**Erectile Dysfunction** - Vardenafil (CYP3A5)
3706	**Bladder Control** - Tolterodine (CYP2D6)

New Tests Released in 2017

Inherited Cardiac Conditions / Cardiovascular Disease - Whole Blood (ACD Solution A)

1267	Long QT Syndrome by Next Generation Sequencing (KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP9, SNTA1, ANK2, CALM1, CALM2, KCNJ5)

Genetic Carrier Screening - **Whole Blood (ACD Solution A) or Mouthwash**

1237	Genetic Carrier Screening Society-Guided Panel (9 genes) includes Bloom Syndrome (BLM), Canavan Disease (ASPA), Cystic Fibrosis Comprehensive Test by Next Generation Sequencing (191 variants of the CFTR gene, including the 23 major mutations approved by ACOG/ACMG) (CFTR), Familial Dysautonomia (IKBKAP), Fanconi Anemia Type C (FANCC), Gaucher Disease (GBA), Mucolipidosis Type IV (MCOLN1), Niemann-Pick Disease (SMPD1), Tay-Sachs Disease (HEXA)
1247	Genetic Carrier Screening Ashkenazi Panel (41 genes) includes Genetic Carrier Screening Society-Guided Panel (9 genes) (ASPA,BLM, CFTR, FANCC, GBA, HEXA, IKBKAP, MCOLN1, SMPD1), Abetalipoproteinemia (MTTP) Alport Syndrome (COL4A3), Arthrogryposis, Mental Retardation, and Seizures (SLC35A3), Bardet-Biedl Syndrome (BBS1, BBS2, BBS10), Carnitine Palmitoyltransferase II Deficiency (CPT2), Congenital Amegakaryocytic Thrombocytopenia (MPL), Congenital Disorder of Glycosylation Type 1a (PMM2), Dyskeratosis Congenita (RTEL1), Ehlers-Danlos Syndrome Type VIIC (ADAMTS2), Familial Hyperinsulinism (ABCC8), Galactosemia (GALT), Glycogen Storage Disease 1a (G6PC), Joubert Syndrome (TMEM216), Maple Syrup Urine Disease Types 1a, 1b, 3 (BCKDHA, BCKDHB, DLD), Multiple Sulfatase Deficiency (SUMF1), Nemaline Myopathy (NEB), Phosphoglycerate Dehydrogenase Deficiency (PHGDH), Polycystic Kidney Disease, Autosomal Recessive (PKHD1), Retinitis Pigmentosa 59 (DHDDS), Smith-Lemli-Opitz Syndrome (DHCR7), Tyrosinemia Type 1 (FAH), Usher Syndrome Type 1F and III (PCDH15, CLRN1), Walker-Warburg Syndrome (FKTN), Wilson Disease (ATP7B), Zellweger Spectrum Disorder (PEX1, PEX2, PEX6)
1248	Bloom Syndrome (BLM)
1249	Canavan Disease (ASPA)
1250	Congenital Amegakaryocytic Thrombocytopenia (MPL)
1251	Familial Dysautonomia (IKBKAP)
1252	Familial Hyperinsulinism (ABCC8)
1253	Fanconi Anemia Type C (FANCC)
1254	Galactosemia (GALT)
1255	Gaucher Disease (GBA)
1256	Glycogen Storage Disease 1a (G6PC)
1257	Maple Syrup Urine Disease Type 1b (BCKDHB)
1258	Mucolipidosis Type IV (MCOLN1)
1259	Nemaline Myopathy (NEB)
1260	Niemann-Pick Disease (SMPD1)
1261	Tay-Sachs Disease (HEXA)
1262	Usher Syndrome Type 1F (PCDH15)
1269	Usher Syndrome Type III (CLRN1)

***BRCA*care® Testing - Whole Blood (ACD Solution A) or Mouthwash**

1241	Comprehensive Hereditary Breast and Gynecologic Cancer Panel: 19 genes analyzed by Gene Sequencing and/or Deletion/Duplication Analysis (BRCA1, BRCA2, ATM, BARD1, BRIP1, CDH1, CHEK2, MUTYH, PALB2, PTEN, RAD51C, RAD51D, STK11, TP53, EPCAM, MLH1, MSH2, MSH6, PMS2)
1243	*BRCA1/2*: Ashkenazi Jewish 3-site Mutation Analysis (Reflex to Comprehensive Hereditary Breast and Gynecologic Cancer Panel) (*If the Ashkenazi Jewish 3-site Mutation Analysis is negative, reflex to 1241.)

***Pharmacogenomics* Testing - Whole Blood (ACD Solution A) - CARDIOLOGY**

3101	**Antiplatelet Agents** - Aspirin, Cilostazol, Clopidogrel, Prasugrel, Ticagrelor (ABCB1, CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, ITGB3, SLOC1B1)
3102	**Statins** -Atorvastatin, Fluvastatin, Lovastatin, Pitavastatin, Pravastatin, Rosuvastatin, Simvastatin (ABCB1, ABCG2, APOE, CYP2C9, CYP2D6, CYP3A4, CYP3A5, KIF6, SLCO1B1)
3103	**Anticlotting Agents** - Acenocoumarol, Coumarol, Fluindione, Phenprocoumon, Warfarin (CYP2C9, CYP2C19, CYP2D6, VKORC1)
3104	**Thrombophilia** - Susceptibility to Factor II, Factor V Leiden (F2, F5, MTHFR)
3105	**Calcium Channel Blockers** - Amlodipine, Nifedipine (CYP3A4, CYP3A5)
3106	**Beta Blockers** - Bufuralol, Carvedilol, Metoprolol, Propranalol, Talinolol, Timolol (ABCB1, CYP2D6, UGT1A1)
3107	**Congestive Heart Failure** - Digoxin (ABCB1)
3108	**Antiarrhythmics** - Flecainide, Propafenone (CYP2D6)
3109	**Antihypertensives** - Benazepril, Debrisoquine, Enalapril, Irbesartan, Losartan, Olmesartan, Verapamil (ABCB1, CYP2D6, CYP2C9, MTHFR, SLOC1B1)

***Pharmacogenomics* Testing - Whole Blood (ACD Solution A) - PAIN MANAGEMENT**

3201	**Pain Management - General** - Alfentanil, Codeine, Fentanyl, Hydrocodone, Ketamine, Methadone, Morphine, Opioids (gen), Oxycodone, Sumatriptan,Tramadol (ABCB1, COMT, CYP2B6, CYP2D6, CYP3A4, DBH, OPRD1, OPRM1)
3202	**Sedatives and Relaxants, including muscle relaxants** - Carisoprodol, Midazolam, Propofol, Rocuronium, Tolperisone (CYP2B6, CYP2C19, CYP2D6, CYP3A4, CYP3A5, SLCO1B1)

Continued From.....pg 2

Therefore, a strong understanding of the patient's pharmacogenomics in prescribing these and other prodrugs is very likely to prevent misprescribing, and may be useful, particularly in clinical circumstances where the consequences may not be immediately visible.

The MDL Pharmacogenomics Solution

Pharmacogenomics testing developed by Medical Diagnostic Laboratories, L.L.C. (MDL) is based upon more than 190 commonly prescribed drugs in 12 prescribing categories. Therapeutic areas covered include cardiology, depression and pain management, as well as less common areas such as attention deficit disorder, inflammatory disorders, and addiction management among others. Testing can be ordered by panels which group together similar drugs or by individual drug.

While we will file all insurances, we will inform the patient if their out-of-pocket expense (including out-of-pocket deductibles) will exceed $150.00. In this way, we keep the patient informed and in control of their healthcare costs. However, we understand that these costs are important, and so patient costs will never be more than $150 per panel, and may be less depending on the genes used to evaluate that panel. Upon request, we will also will run additional panels up to one year after initial receipt of the specimen, without the provider needing to send a new specimen.

What do results look like, and what do they tell you?

Unlike many pharmacogenomics tests in the marketplace, the MDL Pharmacogenomics Solution will never try to tell you what you should, or should not, prescribe for your patient. We believe that you know your patient better than anyone, and so have configured our pharmacogenomics test in a way that lets you use their relevant genetic information in the context of everything else you know about them. So the information on our report is designed so that it can be useful in determining whether to prescribe a drug, or how to monitor your patients' progress on that drug, irrespective of our recommendation.

We provide the pharmacogenomics analysis of the patient in three sections, of increasing detail. In the first section, a color-coded summary report provides simple graphical summary of the patient's analysis (**Figure 6**):

- **Red: Consider Alternate Drug or Dose**
- **Yellow: Consider Alternate Dose**
- **Green: Consider Standard Treatment**

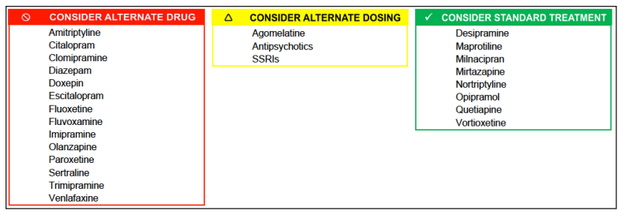


Figure 6. Sample color-coded summary report that appears on the first page of an MDL Pharmacogenomics testing result report.

The summary report is followed by a Comprehensive Interpretation of the analysis, which reviews the test(s) requested, genes examined, general statements about the patient's pharmacogenomic status, likely toxicities, and a formal statement on our recommendations for each drug requested. Potential effects on heart function or drug/drug interactions are listed separately for emphasis (**Figure 7**).

Finally, we provide a detailed breakdown of the results for each drug, describing the gene tested, the genotype observed, and our recommendation. This comprehensive report which provides the name of the drug, the gene, and its genotype, can be used in combination with additional factors know to the ordering physician (i.e. age, sex, weight, smoking status, etc.), to develop a final, personalized precision medicine decision (**Figure 8**).

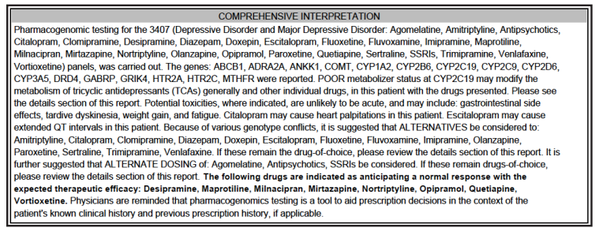
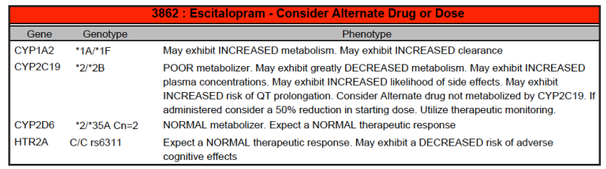


Figure 7. Sample comprehensive interpretation that appears in an MDL Pharmacogenomics testing result report.

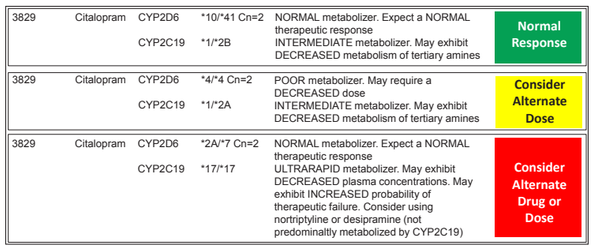


3862 : Escitalopram - Consider Alternate Drug or Dose		
Gene	Genotype	Phenotype
CYP1A2	*1A/*1F	May exhibit INCREASED metabolism. May exhibit INCREASED clearance
CYP2C19	*2/*2B	POOR metabolizer. May exhibit greatly DECREASED metabolism. May exhibit INCREASED plasma concentrations. May exhibit INCREASED likelihood of side effects. May exhibit INCREASED risk of QT prolongation. Consider Alternate drug not metabolized by CYP2C19. If administered consider a 50% reduction in starting dose. Utilize therapeutic monitoring.
CYP2D6	*2/*35A Cn=2	NORMAL metabolizer. Expect a NORMAL therapeutic response
HTR2A	C/C rs6311	Expect a NORMAL therapeutic response. May exhibit a DECREASED risk of adverse cognitive effects

Figure 8. Sample detailed breakdown of each drug that appears in an MDL Pharmacogenomics testing result report.

Why do drugs get put in different boxes?

It is interesting to see how a drug's color-code can vary depending on the genotype of the patient. Let's consider Citalopram as an example. Citalopram is one of the most commonly prescribed anti-depressants, in the Selective Serotonin Reuptake Inhibitor (SSRI) class. In **Figure 9** you can see how the genotypes at CYP2D6 and CYP2C19 greatly influence the potential metabolism of this drug, and hence its potential color-code recommendation.



3829	Citalopram	CYP2D6 CYP2C19	*10/*41 Cn=2 *1/*2B	NORMAL metabolizer. Expect a NORMAL therapeutic response INTERMEDIATE metabolizer. May exhibit DECREASED metabolism of tertiary amines	Normal Response
3829	Citalopram	CYP2D6 CYP2C19	*4/*4 Cn=2 *1/*2A	POOR metabolizer. May require a DECREASED dose INTERMEDIATE metabolizer. May exhibit DECREASED metabolism of tertiary amines	Consider Alternate Dose
3829	Citalopram	CYP2D6 CYP2C19	*2A/*7 Cn=2 *17/*17	NORMAL metabolizer. Expect a NORMAL therapeutic response ULTRARAPID metabolizer. May exhibit DECREASED plasma concentrations. May exhibit INCREASED probability of therapeutic failure. Consider using nortriptyline or desipramine (not predominaltly metabolized by CYP2C19)	Consider Alternate Drug or Dose

Figure 9. Sample color-coded drug-specific interpretation that appears in an MDL Pharmacogenomics testing result report.

The first example shows a patient who is a normal metabolizer at CYP2D6, and an intermediate metabolizer at CYP2C19. In this patient, one would expect a normal response balance between dose (ingestion) and excretion (metabolism) and therefore the color code is green as a normal response is expected. The second example shows a patient who has two null alleles at CYP2D6. Thus, a significant part of their ability to metabolize citalopram is compromised and it is possible that they will gradually accumulate the drug. The yellow designation lets the physician know that while the drug will be effective, they may wish to either start at a lower dose or that the patient may tolerate a lower dose once efficacy has been demonstrated. The third example is a patient with the opposite genetic potential to patient 2. In this example, there is normal metabolizer status at CYP2D6, however, they are a CYP2C19 ultrarapid metabolizer because they have two copies of the *17 rapid metabolizer version of this enzyme. In this case, it is likely to be very difficult to maintain an effective titer of citalopram resulting in a very low probability of drug efficacy. In this case, the red designation indicates that the physician may want to consider an alternative drug that is not metabolized by CYP2C19, and examples are given.

It should be pointed out that citalopram, and its sister drug escitalopram, are amongst the most common with genetically defined potential cardiac side effects. Such side effects always trigger a red designation in order to bring this to the provider's attention. For example, Poor Metabolizer status

Continued.....pg 5

Quality Assurance Q&A

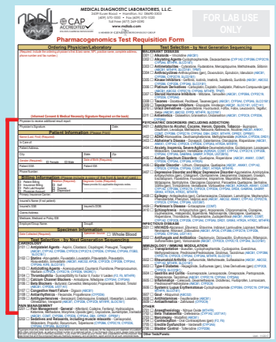
Question:

When I submitted a specimen for Pharmacogenomics testing I was contacted by your Specimen Resolution Center (SRC) because something was missing from the paperwork. What can I do in the future to prevent this?

Answer:

When submitting a whole blood specimen collected in an ACD solution A vial, there are two documents that must be submitted:

- **Pharmacogenomics Test Requisition Form**: In addition to completing the patient and billing information on the front of the test requisition form, the physician MUST sign the Confirmation of Informed Consent and Medical Necessity section on the back.
- **Informed Consent Form**: There is a separate Informed Consent form that must be completed by the patient. The second page of this form must be signed by the patient as indicated and should be submitted along with the completed test requisition form when sending in any specimen for Pharmacogenomic testing.



MEDICAL DIAGNOSTIC LABORATORIES, L.L.C.

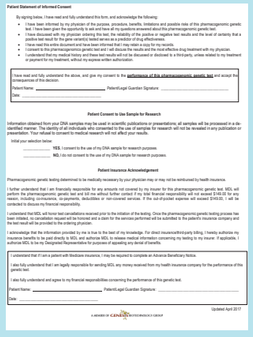
Pharmacogenomics Test Requisition Form

FOR LAB USE ONLY

Tests by Drug

MEDICAL DIAGNOSTIC LABORATORIES, LLC

PATIENT INFORMED CONSENT AND INSURANCE ACKNOWLEDGMENT



Patient Statement of Informed Consent

If you have a question you would like addressed in future issues, please email your question(s) to QAQ&A@mdlab.com.

Journal Watch

Torrellas C, Carril JC, Cacabelos R. 2017. Optimization of Antidepressant use with Pharmacogenetic Strategies. *Curr Genomics* 18(5):442-449

The pharmacogenomic profile of 291 patients undergoing antidepressant treatment without prior pharmacogemomic testing, was determined a CYP2D6, CYP2C9, CYP2C19, CYP3A4 and CYP3A5. 70% of patients were shown to be taking drugs incompatible with their PGx profile. Including this information in prescribing decisions let to efficacy being raised to 80% with 30% complete remission. The authors conclude that, "the prescription of pharmacogenetic profile-based strategies has a positive effect on the therapeutic response to antidepressants"

Bradley P, Shiekh M, Mehra V, et al. 2017. Improved efficacy with targeted pharmacogenetic-guided treatment of patients with depression and anxiety: A randomized clinical trial demonstrating clinical utility. *J Psychiatr Res* 23;96: 100-107

The authors conducted a prospective, double-blind, randomized trial of 685 patients. A panel of 10 genes was tested on over 40 drugs used from the treatment of depression and anxiety. The pharmacogenomic testing was carried out at the initial visit, along with a clinical assessment. Control subjects were treated with "standard of care" and experimental subjects were treated according to their PGx profile. In addition to several positive outcomes, in the experimental group at 12 weeks response and remission rates were significantly higher in the PGx-guided group ($p = 0.001$; OR = 4.72 and $p = 0.02$, OR = 3.54, respectively). The Authors concluded that, "…PGx-guided medication selection significantly improves outcome."

Borse MS, Dong OM, Polasek MJ, et al. 2017. CYP2C19-guided antiplatelet therapy: a cost-effectiveness analysis of 30-day and 1-year outcomes following percutaneous coronary intervention. *Pharmacogenomics* 18(12): 1155-1166.

The authors determined the utility of CYP2C19 testing in prescribing antiplatelet therapy. The control group received regular clopidogrel or prasugrel. The experimental group received PGx-guided therapy. Overall, the groups were monitored for subsequent major cardiovascular and/or bleeding events. In the control group, the overall cost of such events was $42,198 and in the PGx group it was $8,525. The authors concluded that, "… implementing a CYP2C19 genotype-guided approach to antiplatelet therapy could have a positive economic impact…"

Brown LC, Lorenz RA, Li J, et al. Economic utility: Combinatorial pharmacogenomics and medication cost savings for mental health care in a primary care setting. *Clin Ther* 39(3): 592-602.

The authors conducted a pharmacogenomics analysis to evaluate potential cost savings over the course of a 1-year treatment program in mental illness. 2,168 patients were subjected to PGx testing and their pharmacy costs were compared before and after testing. Treatment administered according to PGx testing led to average savings of $3,988 per patient, compared to costs before treatment. The authors conclude that, "… Healthcare providers treating patients with mental illness can significantly reduce medication costs by following PGx report recommendations…"

Continued From.....pg 3

at CYP2C19 may predispose to QT interval elongation with citalopram and escitalopram, and G/G homozygosity at HTR2A may cause heart palpitations with citalopram.

In another field (cardiology) prescription of statins may be associated with muscle pain, and the patient's pharmacogenomics profile may help bring this to light. For example, atorvastatin (generic Lipitor), may be more likely to cause myalgia in the context of the CYP3A5 allele, *3 . Similarly, T/T homozygosity at one of the SLCO1B1 loci may predict a drug-drug reactivity with co-administered rifampin, that will lead to elevated serum levels of atorvastatin. In either case, the provider will now have information to guide prescribing or post-prescribing monitoring, that was previously unavailable. Similarly, the presence of the *1F allele at CYP1A2 may inhibit creation of the active form of the prodrug clopidogrel (generic Plavix), leading to lower therapeutic benefit and higher platelet reactivity, than expected when the administered dose alone is considered. Each of those examples would position the drugs into a red designation, and in both cases, alternative drugs are available for consideration.

In a final example, the presence of A/A homozygosity at the opioid receptor OPRM1 may lead to increased sensitivity to a range of pain medications such as morphine, fentanyl, tramadol, and opioid analgesics generally. In the presence of this genotype, providers may consider a lower starting dose, or reducing dose once efficacy has been established. The presence of this information in the detailed report would be indicated by these drugs having a yellow designation on the summary report.

How can you use the information the test provides?

MDL does not believe that we should tell providers what they should or should not prescribe. Rather, we wish to provide practitioners with information that may be useful to them in making prescribing decisions, or in working with patients after prescribing the drug. This philosophy may result in fewer drugs carrying the green designation than with other testing laboratories. However, we believe that it is the practitioner who should make determinations about the importance of a side effect, because they know all of the various aspects of the individual patient for whom the test was ordered.

Pharmacogenomics testing represents the cutting edge of prescribing. It is not a tool designed for every patient, nor will it fit the needs of every provider. However, in a situation where a personalized, precision medicine approach is necessary, it may provide a key tool in the providers' toolbox.

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2. **Winner JG, Carhart JM, Altar CA, et al.** 2013. A prospective, randomized, double-blind study assessing the clinical impact of integrated pharmacogenomic testing for major depressive disorder. *Discov Med* **16(89)**:219-27.
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4. **Olson MC, Maciel A, Gariepy JF, et al.** 2017. Clinical Impact of Pharmacogenetic-Guided Treatment for Patients Exhibiting Neuropsychiatric Disorders: A Randomized Controlled Trial. *Prim Care Companion CNS Disord.* **19(2)**.
5. **Hornberger J, Li Q, Quinn B.** 2015. Cost-effectiveness of combinatorial pharmacogenomic testing for treatment-resistant major depressive disorder patients. *Am J Manag Care* **21(6)**:e357-65.
6. Use of Codeine and Tramadol Products in Breastfeeding Women - FDA. https://www.fda.gov/Drugs/DrugSafety/ucm118113.htm Accessed November 8, 2017.

Recent Publications

Institute for Metabolic Disorders:

1. **McCourt P, Liu HY, Parker JE, Gallo-Ebert C, Donigan M, Bata A, Giordano C, Kelly SL, Nickels JT Jr.** 2016. Proper Sterol Distribution Is Required for *Candida albicans* Hyphal Formation and Virulence. *G3 (Bethesda)*. 2016 Aug 31. *[Epub ahead of print]* PMID: 27587298
2. **Villasmil ML, Gallo-Ebert C, Liu HY, Francisco J, Nickels JT Jr.** 2017. A link between very long chain fatty acid elongation and mating-specific yeast cell cycle arrest. *Cell Cycle*. 2017 July 26. [Epub ahead of print] PMID: 28745545

Femeris Women's Health Research Center:

1. **Ventolini G, Khandelwal N, Hutton K, Lugo J, Gygax SE, Schlabritz-Loutsevitch N.** 2017. Obesity and recurrent vulvovaginal bacterial infections in women of reproductive age. *Postgrad Med J* 93(1099):297. PMID: 28057837
2. **Hilbert DW, Schuyler JA, Adelson ME, Mordechai E, Sobel JD, Gygax SE.** 2017. *Gardnerella vaginalis* population dynamics in bacterial vaginosis. *Eur J Clin Microbiol Infect Dis* 36(7):1269-1278. PMID: 28197729