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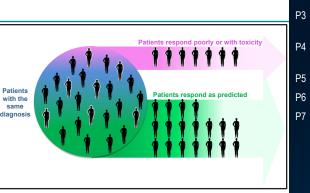
Pharmacogenomics:

What is it, and how should you use it?

By: Grant Gallagher, Ph.D. Institute for Senior Team Leader Research Institute for Biomarker Research

What is Pharmacogenomics?

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.



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.

(p<0.007) (3).

	WINTER 2017 VOLUME 10 No. 1 Yearly Public	^{ition} P6	New Tests in 2017	P5	Recent Publications	P4	Q&A Section, & Journal Watch
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41351157	Glass-25 x 75mm-90° Ground Edges-Plain-72/Be	ox (10 Gross)	20 bx/cs	\$75.97
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41351237	Diamond White Glass-25 x 75mm-Charged-90° (Aqua Frosted-72 Slides/Pack (10 Gross)	Ground Edges	20 pk/cs	\$13.97
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41351253	Diamond White Glass-25 x 75mm-Charged-90° (White Frosted	Ground Edges	72/bx	\$260.97
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	<u>е</u> питаенук Рагt No. 71011000 71011001	Description Extra-Small Small	POWDER-F NITRILE G Quantity 1000/case 1000/case	REE LOVES Price \$64.00 \$64.00

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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

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

same diagnosis and determine who amongst them will respond to a given drug as expected, and who will not.

How Well Does it Work?

In 2017, Perez et al conducted a randomized, double-blind controlled trial of 316 patients requiring antidepressants. The Pharmacogenomics-guided group had a higher 12week 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 PGxguided 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 PGxguided 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

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....

WHAT'S INSIDE

- Pharmacogenomics. Continued
- Pharmacogenomics. Continued
- Q&A Section, & Journal Watch
- Recent Publications
- New Tests Released
- WWMP Deals



Pharmacogenomics: What is it, and how should you use it?

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 PGxguided 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 pharmacogenomicsguided 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 commonlyprescribed 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 gentovpe 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 higherthan-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

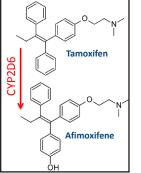
Prodrugs are common. Examples in three fields (malignant disease, platelet inhibition, and pain management) can illustrate this:

ACTIVE DRUG PRODRUG Poor Metabolizer Poor Metabolizer Effective concentration May not reach an may be too high effective concentration Rapid Metabolizer Rapid Metabolizer May not reach an Effective concentration effective concentration may be too high

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 postsurgical 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).



Continued From.....pg 1

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.

2 ovo Clonida

Codeine, and a number of its derivatives, are analgesic and antitussive agents, based on

Figure 5. Chemical structure of codeine

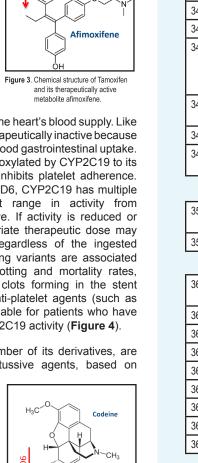
. metabolite morphine

and it's therapeutically active

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...pa 3

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).



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

3301	Ikaloids – Vincristine (ABCB1)
3302	Alkylating Agents-Cyclophosphamide, Dacacarbazine (CYP1A2, CYP2B6, CY
3303	Antimetabolites - Cytarabine, Fludarabine, Mercaptopurine, Methotrexate, Silib
3304	Anthracyclines-Anthracyclines (gen), Doxorubicin, Epirubicin, Idarubicin (ABCE
305	Kinase Inhibitors - Gefitinib, Icotinib, Imatinib, Sorafenib, Sunitinib (ABCB1, AB
3306	Platinum Derivatives - Carboplatin, Cisplatin, Oxaliplatin, Platinum Compounds
307	Steroid Hormone Inhibitors - Mitotane, Tamoxifen (ABCB1, CYP2B6, CYP2C1
308	Taxanes - Docetaxel, Paclitaxel, Taxanes (gen) (ABCB1, CYP3A4, CYP3A5, SL
3309	Topoisomerase Inhibitors - Etoposide, Irinotecan (ABCB1, SLOC1B1, UGT1A
3310	Uracil Derivatives - Capecitabine, Fluorouracil, Folfox, Folox, Leucovorin, Tega
3311	Antiemetics - Dolasetron, Granisetron, Ondansetron (ABCB1, CYP2C9, CYP2
	PSYCHIATRIC DISORDERS (INCLUDING ADDICTION)
401	Addiction to Alcohol, Cocaine, Heroin, Opioids, Tobacco - Bupropion, Disulf CYP2C19, CYP3A4, DBH, DRD1, MTHFR, OPRD1, OPRM1)
3402	ADHD-Atomoxetine, Dextroamphetamine, Methylphenidate (ADRA2A, CYP2D6
3403	Alzheimer's Disease - Donepezil, Galantamine, Olanzapine, Risperidone (ABC
3404	Anxiety, Insomnia, Severe Agitation-Dexmedetomidine, Escitalopram, Loraze CYP3A4, CYP3A5, GABRA6, GABRP, HTR2A, UGT2B15)
3405	Autism Spectrum Disorders - Quetiapine, Risperidone (ABCB1, ANKK1, COM
3406	Bipolar Disorder - Lithium, Olanzapine, Quetiapine (ABCB1, ANKK1, CYP1A2,
407	Depressive Disorder and Major Depressive Disorder-Agomelatine, Amitriptyl Escitalopram, Fluoexitine, Fluvoxamine, Imipramine, Maprotiline, Milnacipran, M Trimipramine, Venlafaxine, Vortioxetine (ABCB1, ADRA2A, ANKK1, COMT, CYF HTR2A, HTR2C, MTHFR)
3408	Epilepsy - Antiepileptics (gen), Carbamazepine, Clobazam, Lamotrigine, Mephe CYP2C9, CYP3A4, CYP3A5, UGT2B7)
3409	Parkinson's Disease - Entacaptone (COMT)
3410	Schizophrenia - Antipsychotics (gen), Aripiprazole, Chlorpromazine, Clozapine, Thioridazine, Trifluoperazine, Zuclopenthixol (ABCB1, ANKK1, COMT, CYP1A2,
	INFECTIOUS DISEASE
3501	HIV/AIDS-Atazanavir, Efavirenz, Etravirine, Indinavir, Lamivudine, Lopinavir, Net CYP3A4, CYP3A5, UGT1A1)
3502	Antifungals and Antibiotics - Daptomycin, Dicloxacillin, Erythromycin, Rifampi
	IMMUNOLOGY / IMMUNE MODULATION
3601	Transplantation - Busulfan, Cyclophosphamide, Cyclosporine, Everolimus, Met CYP2C9, CYP3A4, CYP3A5, MTHFR, SLCO1B1)
3602	Rheumatoid Arthritis - Leflunomide, Methotrexate, Sulfasalazine (ABCB1, ABC
3603	Type-II Diabetes - Repaglinide, Sulfoureas (gen), Urea Derivatives (gen) (CYP2
3604	Gastritis and Colitis - Esomeprazole, Lansoprazole, Omeprazole, Pantoprazol
3605	nflammation - Celecoxib, Dexamethasone, Diclofenac, Flurbiprofen, Lornoxicar
3606	Systemic Lupus Erythematosus-Cyclophosphamide (CYP2B6, CYP2C19, CY
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)
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YP2C19, CYP3A4, MTHFR, SLCO1B1)

ibinin (ABCB1, MTHFR, SLCO1B1, TPMT)

B1, CYP2B6, CYP2C19, SLCO1B1)

BCG2, CYP2B6, CYP2D6, CYP3A5, SLCO1B1)

ds (gen) (ABCB1, ABCG2, CYP2C19, CYP3A5, MTHFR, TPMT)

(19, CYP2D6, CYP3A4)

LCO1B1)

A1)

afur. Xelox (ABCB1, ABCG2, DYPD, MTHFR, SLCO1B1)

2D6,CYP3A5)

lfiram, Levodopa, Methadone, Naloxone, Naltrexone, Nicotine (ABCB1, ANKK1, COMT, CYP2B6,

6. DRD1)

CB1, ANKK1, CYP1A2, CYP2C9, CYP2D6, CYP3A5, HTR2A, MTHFR)

epam, Midazolam, Oxazepam, Venlafaxine (ADRA2A, COMT, CYP1A2, CYP2C19, CYP2D6,

MT. CYP2D6, CYP3A4, CYP3A5, HTR2A)

, CYP2C9, CYP2D6, CYP3A5, COMT, DRD1, HTR2A, MTHFR)

line, Antipsychotics (gen), Citalopram, Clomipramine, Desipramine, Diazepam, Doxepin, Mirtazapine, Nortriptyline, Olanzapine, Opipramol, Paroxetine, Quetiapine, Sertraline, SSRIs (gen), P1A2, CYP2B6, CYP2C19, CYP2C9, CYP2D6, CYP3A5, DRD4, GABRA6, GABRP, GRIK4,

nenytoin, Phenobarbital, Phenytoin, Valproic acid (ABCB1, ABCG2, ANKK1, CYP1A2, CYP2C19,

e, Fluphenazine, Haloperidol, Iloperidone, Nemonapride, Olanzapine, Quetiapine, Risperidone, CYP2C9, CYP2D6, CYP3A4, CYP3A5, DRD1, GRIK4, HTR2A, HTR2C, MTHFR)

elfinavir, Nevirapine, Ritonavir, Zidovudine (ABCB1, APOE, CYP2B6, CYP2C19, CYP2D6,

picin, Sulfonamides (gen), Voriconazole (ABCB1, CYP2C9, CYP2C19, CYP3A4, SLCO1B1)

ethylprednisone, Prednisone/Prednisolone, Sirolimus, Tacrolimus (ABCB1, CYP2B6, CYP2C19,

CG2. CYP1A2. MTHFR. SLCO1B1)

2C8, CYP2C9, SLCO1B1)

ole, Rabeprazole, Tacrolimus (ABCB1, CYP2C19, CYP3A4, CYP3A5)

am, Prednisone/Prednisolone (ABCB1, CYP2C9)

YP3A4, MTHFR, SLCO1B1)

New Tests Released in 2017

Inherited Cardiac Conditions	/ Cardiovascular Disease -	Whole Blood (ACD Solution A)
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Long QT Syndrome by Next Generation Sequencing (KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ2, CACNA1C, 1267 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)

BRCAcare® Testing - Whole Blood (ACD Solution A) or Mouthwash

Analysis is negative, reflex to 1241.)

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	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

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)
	Reserves and the Testing Wheth Divertige 0.1 (1.1.0) BAIN MANA OF MENT

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

3202	Sadatives and Pelavants including muscle relevants - Carisoprodel Midazolam Proposal Recurptium Tolparisope (CVP286, CVP2010, CVP206, CVP304, CVP304, CVP305
	COMT, CYP2B6, CYP2D6, CYP3A4, DBH, OPRD1, OPRM1)
3201	Pain Management - General - Alfentanil, Codeine, Fentanyl, Hydrocodone, Ketamine, Methadone, Morphine, Opioids (gen), Oxycodone, Sumatriptan, Tramadol (ABCB1,

Idazolam, Propotol, Rocuronium, Tolperisone (CYP2B6, CYP2C19, CYP2D6, CYP3A4, CYP3A5 segatives SLCO1B1)

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?

It is interesting to see how a drug's color-code can vary depending on Unlike many pharmacogenomics tests in the marketplace, the MDL the genotype of the patient. Let's consider Citalopram as an example. Pharmacogenomics Solution will never try to tell you what you should, or Citalopram is one of the most commonly prescribed anti-depressants, in should not, prescribe for your patient. We believe that you know your patient the Selective Serotonin Reuptake Inhibitor (SSRI) class. In Figure 9 you better than anyone, and so have configured our pharmacogenomics test in can see how the genotypes at CYP2D6 and CYP2C19 greatly influence a way that lets you use their relevant genetic information in the context of the potential metabolism of this drug, and hence its potential color-code everything else you know about them. So the information on our report recommendation 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

0	CONSIDER ALTERNATE DRUG	CONSIDER ALTERNATE DOSING	1	CONSIDER STANDARD TREATM
			· ·	
	Amitriptyline	Agomelatine		Desipramine
	Citalopram	Antipsychotics		Maprotiline
	Clomipramine	SSRIs		Milnacipran
	Diazepam			Mirtazapine
	Doxepin			Nortriptyline
	Escitalopram			Opipramol
	Fluoxetine			Quetiapine
	Fluvoxamine			Vortioxetine
	Imipramine			
	Olanzapine			
	Paroxetine			
	Sertraline			
	Trimipramine			
	Venlafaxine			

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 not metabolized by CYP2C19, and examples are given. recommendation. This comprehensive report which provides the name of the drug, the gene, and its genotype, can be used in combination with It should be pointed out that citalopram, and its sister drug escitalopram, additional factors know to the ordering physician (i.e. age, sex, weight, are amongst the most common with genetically defined potential cardiac smoking status, etc.), to develop a final, personalized precision medicine side effects. Such side effects always trigger a red designation in order to decision (Figure 8). bring this to the provider's attention. For example, Poor Metabolizer status

Pharmacogenomic testing for the 3407 (Depressive Disorder and Major Depressive Disorder: Agomelatine, Amitriptyline, Antipsychotics, Citalopram, Clomipramine, Desipramine, Diazepam, Doxepin, Escitalopram, Fluoxetine, Fluvoxamine, Imipramine, Maprotiline, Milnacipran, Mirtazapine, Nortriptyline, Olanzapine, Opipramol, Paroxetine, Quetiapine, Sertraline, SSRIs, Trimipramine, Venlafaxin minicipality in microphysics, which will be a set of the set of metabolism of tricyclic antidepressants (TCAs) generally and other individual drugs, in this patient with the drugs presented. Please see the details section of this report. Potential toxicities, where indicated, are unlikely to be acute, and may include: gastrointestinal side effects, tardive dyskinesia, weight gain, and fatigue. Citalopram may cause heart palpitations in this patient. Escitalopram may cause and/cc, indiver dystatesia, weight gain, and laugue. Cliatophant may cause heart paphatons in this patient. Excatalophant may cause extended QT intervals in this patient. Excatalophant may cause extended QT intervals in this patient. Because of various genotype conflicts, it is suggested that ALTERNATIVES be considered to: Amitriptyline, Citalopram, Clomipramine, Diazepam, Doxepin, Escitalopram, Fluxostine, Fluxostine, Inipramine, Olarzapine, Paroxetine, Sertraline, Trimipramine, Venafaxine. If these remain the drug-of-choice, please review the details section of this report. It is further suggested that ALTERNATE DOSING of: Agomelatine, Antipsychotics, SSRIs be considered. If these remain drugs-of-choice, anies augusted unit activation to reproduce the provided of the provided and the provided of t

COMPREHENSIVE INTERPRETATION

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. 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?

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	*4/*4 Cn=2	POOR metabolizer. May require a DECREASED dose	Consider
		CYP2C19 *	*1/*2A	INTERMEDIATE metabolizer. May exhibit DECREASED metabolism of tertiary amine	Alternate Dose
3829	Citalopram	CYP2D6	*2A/*7 Cn=2	NORMAL metabolizer. Expect a NORMAL therapeutic response	
		CYP2C19	*17/*17	ULTRARAPID metabolizer. May exhibit DECREASED plasma concentrations. May exhibit INCREASED probability of therapeutic failure. Consider using nortripyline or designamine (not predominality 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 vellow 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

3

Pharmacogenomics: What is it, and how should you use it?



Quality Assurance

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 Reguisition 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.

C. MEDICAL DIAGNOSTIC LABORATORIES, LL.C.	Tests by Drug		
	2021 C Aperocamenti 2011 C Deblessaire 2021 C Gebico 2021 C Nalssone 2020 C Rocursian	appli	Patient Statement of Informed Consent
FOR LAB USE	302 □ Aponelative 2842 □ Delecatios 2802 □ Ganiseton 3022 □ Nativecore 2802 □ Rosvertation 3023 □ Alectani 2842 □ Delecatios 2803 □ Halcontol 3023 □ Nethnavir 2803 □ Setosine	MEDICAL DIAGNOSTIC LABORATORIES, LLC	By signing below. I have read and fully understand this form, and acknowledge the following:
ACCREDITED www.indub.com	30H D Alcourini 30H D Deamethacce 30H D Hydrocolone 30H D Nemorapide 39H D Sibbin		 I have been informed by my obvician of the purpose, properties, imitations and possible risks of this pharmacoperantic penetic.
CONTRACTOR CONTRACTOR CONTRACTOR	MMC C Amindaine 386 C Destrumphenine MMC C Manifolds 2026 C Notifier 286 C Signifiant	-	test. I have been given the opportunity to ask and have all my questions answered about this pharmacogenomic genetic test.
Pharmacogenomics Test Requisition Form		PATIENT INFORMED CONSENT AND INSURANCE ACKNOWLEDGEMENT	 These decursed with my physician ordering this test, the reliability of the positive or negative test neutra and the level of certainty that a positive test multi for the pane variantial tested annex as a predictor of drug effectiveness.
Ordering Physician Laboratory Text Selection - by Next Generation Sequencing	1990 C Anteparticipant (Mrs C Advance) 1990 C Interaction 2829 C Notables 2990 C Subscience		 have read this entire document and have been informed that I may relatin a copy for my records.
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	T40.4XSA Adverse effect of other synthetic narcolic, initial encounter the point source without further testing without further in the source of the source		
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If you have a question you would like addressed in future issues, please email your question(s) to QAQ&A@mdlab.com.

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

OURNAL Watch

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-quided 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..."

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.

Recent Publications



Institute for Metabolic Disorders:

- specific yeast cell cycle arrest. Cell Cycle. 2017 July 26. [Epub ahead of print] PMID: 28745545



- infections in women of reproductive age. Postgrad Med J 93(1099):297. PMID: 28057837
- vaginosis. Eur J Clin Microbiol Infect Dis 36(7):1269-1278. PMID: 28197729

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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.
- 3. Hall-Flavin DK, Winner JG, Allen JD, et al. 2013. Utility of integrated pharmacogenomic testing to support the treatment of major depressive disorder in a psychiatric outpatient setting. *Pharmacogenet Genomics* 23(10):535-48.
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- 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.



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