Personalized Medicine to Improve and Save Lives

Improve effectiveness and minimize risk with MD GeneticPro®

MD GeneticPro®

Advanced Genetic Testing • www.MDGeneticPro.com

Impact Patient Health, Safety and Quality-of-Life.

What is Pharmacogenomics?

Pharmacogenomics (PGx) is the relationship between a patient's inherited genetic makeup and their response to pharmaceutical drugs.

Goals of Pharmacogenomics:

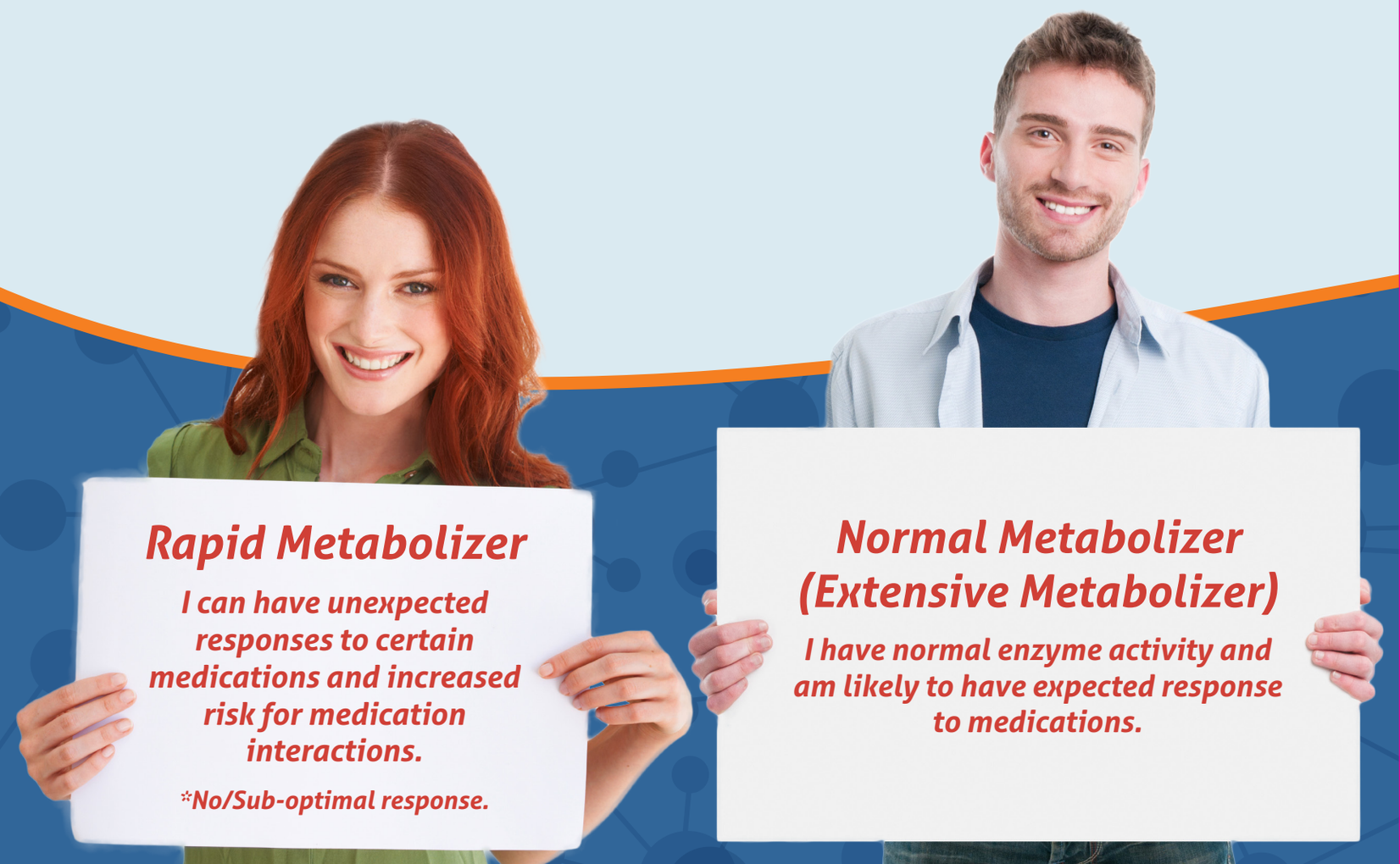
Select Responsive Patients

Avoid Adverse Drug Reactions

Maximize Drug Efficacy

When to Pursue Genetic Testing:

- **Prior** to initiation of therapy when using a drug that's **hard to dose**
- **After** the initiation of therapy when a patient's **not achieving** an expected therapeutic goal



Consequences of Mismanagement:

Adverse Drug Reactions Over 2 Million/Year

Death 4th in US

Illness 5th in US

Cost of Mortality from ADRs **$177 Billion**

Sources: Trescot, et. al. American Society of International Pain Physicians;
FDA Preventable Adverse Drug Reactions: A Focus on Drug Interactions; http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm110632.htm Accessed October 27, 2015.

METABOLISM PROFILE	MEDICATION METABOLISM	PARENT DRUG	METABOLITES	POTENTIAL CLINICAL IMPACT
RAPID	• Significantly increased enzyme activity • Metabolizes certain medications at a significantly higher rate than normal	LOW	HIGH	• Unexpected therapeutic response • Increased risk for adverse effects • Increased risk for medication interactions • Need for dose adjustment • Need for medication change
NORMAL	• Normal enzyme activity • Metabolizes certain medications at a normal rate	NORM	NORM	• Likely to have expected response to medications
INTERMEDIATE	• Reduced enzyme activity • Metabolizes certain medications at a somewhat lower rate than expected	INCREASED	DECREASED	• Minimal effect on therapeutic response and risk for adverse effects
POOR	• No enzyme activity • Metabolizes certain medications at a significantly lower rate than normal	HIGH	LOW	• Unexpected therapeutic response • Increased risk for adverse effects • Increased risk for medication interactions • Need for dose adjustment • Need for medication change

Targeted Therapy

Efficacy and Safety can vary by medication metabolism profile.

MD GeneticPro® Pharmacogenetic Testing :

- *Assesses a number of key drug metabolism enzymes[1]*
- *Identifies the underlying genetic characteristics that impact the metabolism of medications commonly prescribed to patients with pain[1]*
- *Simplifies specimen collection with patient-friendly, saliva-based testing[5]*

Pain Management Drugs:

- ***Only 42% of patients using prescription pain relief medication receive relief.[6]***
- Genetic variations in CYP450 2D6, 3A4, and 3A5 enzymes have been shown to significantly affect responses to various opioids and ***alter clinical outcomes, including likelihood of overdose.[7-8]***
- Prescription opioid pain relievers account for ***more overdose deaths than heroin and cocaine combined - 15,000 vs. 4,000.[9]***
- ***Approximately 10% of the population are Poor Metabolizers, 7% are Ultra-Rapid Metabolizers and 35% are carriers of a non-functional 2D6 allele, elevating the risk of ADRs when these individuals take multiple drugs.***

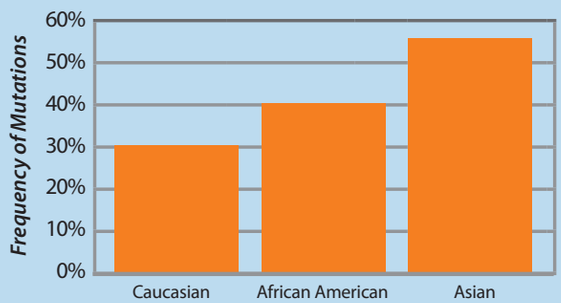
Neuroactive Drugs:

- Approximately ***50% of all patients do not adequately respond to first line medication*** and require lengthy trial and error attempts to identify the appropriate drug.
- Therapeutic benefit typically takes weeks to achieve after stable dosing.
- Testing for genes that are involved in NAD metabolism should be considered when:
  - Starting a patient on a NAS metabolized by CPY2D6, CYP2C19, CYP3A4 or CYP3A5.
  - Pharmacogenetic information exists that suggests concomitant medications may inhibit CPY2D6, CYP2C19, CYP3A4 orCYP3A5 if the patient is taking one or more NAD.
  - Testing for CYP metabolic status can assist physicians in selecting the appropriate NAD choice and dose at the individual patient level.

Improve Outcomes

Clopidogrel (Plavix®):

- ***Clopidogrel is the second-highest selling drug in the world*** with >90 million patients worldwide.[10]
- Up to 30% of patients treated with standard doses of Clopidrogel respond poorly, thus ***increasing their risk of recurrent ischemic events.[10]***
- 2C19 carriers have more than ***50% increased risk of death from cardiovascular causes, MI, or stroke*** compared with non-carriers.[11]
- Patients with variants in 2C19 have a ***3.58 times greater risk for major adverse cardiovascular events such as death, heart attack and stroke.[11]***
- CYP450 2C19 genetic variations are present in ***high percentages of ethnic populations[12]:***



Warfarin:

- ***Warfarin is the most commonly prescribed anticoagulant in the world.***
- The consequences of incorrect dosage are severe and, in some cases, life threatening.
- ***The average bleeding cost associated with Warfarin is $15,998.***
- Patient response to Warfarin has been shown to be influenced by genetic factors.
- 2C9 & VKORC1 genetic variants explain >50% of the patient variability in Warfarin dose response.
- ***Genetic testing could allow Warfarin users to avoid 85,000 serious bleeding events and 17,000 strokes each year...***This could result in a savings of $1.1 billion annually.
- Studies have shown that Warfarin therapy guided by genetic testing led to ***stable anticoagulation in patients 18 days quicker*** than those who followed the average dose protocol.

Sample Report

Premier Medical Laboratory Service (PMLS)
6000A Pelham Road, Greenville, SC 29615
Phone: 877-335-2455
Web: www.premedinc.com
Laboratory Director: Peter Zvejnieks, MD

Comprehensive Pharmacogenetic Report Created for: John Doe

Patient:	John Doe	DOB:	1/1/1962
Accession #:	2345	Gender:	Male
Collection Date:	2/24/2014	Received Date:	2/25/2014
Ordered By:	Dr. Smith	Report Generated:	2/27/2014

Patient Medications

Current Medication List: Plavix, Lopressor

Medications Affected by Patient Genetic Results

Plavix (Clopidogrel) Evidence Level: 2
Significantly Reduced Response to Clopidogrel
Consider alternative therapy. Example of alternative drugs: Prasugrel (contraindicated in TIA/Stroke patients); Ticagrelor; Aspirin; Aspirin plus Dipyridamole.

Lopressor (Metoprolol) Evidence Level: 1
Normal Sensitivity to Metoprolol
Metoprolol can be prescribed at standard label recommended-dosage and administration. Selection of proper dosage requires individual titration.

Test Details

	Assay	Results	Phenotype	Clinical Consequences
	CYP2C19	*7/*7	Poor Metabolizer	Consistent with a significant deficiency in CYP2C19 activity. Increased risk for side effects or loss of efficacy with drug substrates.
	CYP2C9	*2/*2	Poor Metabolizer	Consistent with a significant deficiency in CYP2C9 activity. Increased risk for side effects or loss of efficacy with drug substrates.
	CYP2D6	*1/*1	Normal Metabolizer	Consistent with a typical CYP2D6 activity. This test did not identify risks for side effects or loss of efficacy with drug substrates.
	CYP3A4	*3/*3	Intermediate Metabolizer	Consistent with a a moderate deficiency in CYP3A4 activity. Caution is advised when prescribing narrow therapeutic index drugs. Alternative drugs or dose adjustment may be required if CYP3A inhibitors or inducers are co-prescribed.
	CYP3A5	*3C/*3C	Poor Metabolizer	Consistent with a poor CYP3A5 activity. Caution is advised when prescribing narrow therapeutic index drugs. Alternative drugs or dose adjustment may be required if CYP3A inhibitors or inducers are co-prescribed.
	VKORC1	-1639G>A G/A	Intermediate Warfarin Sensitivity	VKORC1 is the site of action of warfarin. The patient may require a decrease in warfarin dosage.
	Factor II Factor V Leiden	20210G>A GA 1691G>A GG	Increased Thrombosis Risk	The patient's genotypes for Factor V Leiden and Factor II predicts an increased risk for thrombosis. Consider avoiding estrogen-containing preparations. A short course of prophylactic anticoagulation may be considered in high-risk settings such as surgery.
	MTHFR MTHFR	1298A>C AA 677C>T CC	No Increased Risk of Hyperhomocysteinemia	The patient has a normal MTHFR function and no elevation of plasma homocysteine levels is expected. The risk for venous thromboembolism is not increased.
	Apolipoprotein E	ε3/ε4	Increased Risk of Hyperlipidemia/Atherosclerotic Vascular Disease	The patient's has one copy of an abnormal APOE allele, that is associated with an increased risk for hyperlipidemia/atherosclerotic vascular disease.

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Potentially Impacted Medications

Cardiovascular Medications

Standard Precautions	Use With Caution	Consider Alternatives
Carvedilol (Coreg)	Fluvastatin (Lescol)	Clopidogrel (Plavix)
Flecainide (Tambocor)	Warfarin (Coumadin)	
Irbesartan (Avapro)		
Metoprolol (Lopressor)		
Mexiletine (Mexitil)		
Nebivolol (Bystolic)		
Prasugrel (Effient)		
Propafenone (Rythmol)		
Propranolol (Inderal)		
Ticagrelor (Brilinta)		
Timolol (Timoptic)		

Pain Medications

Standard Precautions	Use With Caution	Consider Alternatives
Codeine (Codeine)	Carisoprodol (Soma)	
Hydrocodone (Vicodin)	Celecoxib (Celebrex)	
Oxycodone (Percocet)	Flurbiprofen (Ansaid)	
Tramadol (Ultram)	Piroxicam (Feldene)	

Psychotropic Medications

Standard Precautions	Use With Caution	Consider Alternatives
Aripiprazole (Abilify)	Amitriptyline (Elavil)	
Atomoxetine (Strattera)	Citalopram (Celexa)	
Clozapine (Clozaril)	Clobazam (Onfi)	
Desipramine (Norpramin)	Clomipramine (Anafranil)	
Desvenlafaxine (Pristiq)	Diazepam (Valium)	
Donepezil (Aricept)	Doxepin (Silenor)	
Duloxetine (Cymbalta)	Escitalopram (Lexapro)	
Galantamine (Razadyne)	Imipramine (Tofranil)	
Haloperidol (Haldol)	Phenytoin (Dilantin)	
Iloperidone (Fanapt)	Sertraline (Zoloft)	
Mirtazapine (Remeron)	Tetrabenazine (Xenazine)	
Nortriptyline (Pamelor)	Trimipramine (Surmontil)	
Olanzapine (Zyprexa)		
Paliperidone (Invega)		
Paroxetine (Paxil)		
Perphenazine (Trilafon)		
Pimozide (Orap)		
Risperidone (Risperdal)		
Thioridazine (Mellaril)		
Venlafaxine (Effexor)		

Other Medications

Standard Precautions	Use With Caution	Consider Alternatives
Darifenacin (Enablex)	Glimepiride (Amaryl)	
Dexlansoprazole (Dexilant)	Glipizide (Glucotrol)	
Esomeprazole (Nexium)	Glyburide (Micronase)	
Fesoterodine (Toviaz)	Tolbutamide (Orinase)	
Lansoprazole (Prevacid)	Voriconazole (Vfend)	
Omeprazole (Prilosec)		
Ondansetron (Zofran)		
Pantoprazole (Protonix)		
Rabeprazole (Aciphex)		
Tacrolimus (Prograf)		
Tamsulosin (Flomax)		
Tolterodine (Detrol)		

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Dosing Guidance

Amitriptyline (Elavil) Evidence Level: 1

Increased Sensitivity to Amitriptyline (CYP2C19 *7/*7 Poor Metabolizer)

Consider a 50% reduction of recommended amitriptyline starting dose and monitor the plasma concentrations of amitriptyline and nortriptyline to adjust the dose.

Carisoprodol (Soma) Evidence Level: 1

Altered Sensitivity to Carisoprodol (CYP2C19 *7/*7 Poor Metabolizer)

Carisoprodol should be used with caution in patients with reduced CYP2C19 activity. Because there is insufficient data to allow calculation of dose adjustment when carisoprodol is prescribed, consider reducing the dose or consider using an alternative therapy.

Celecoxib (Celebrex) Evidence Level: 1

High Sensitivity to Celecoxib (CYP2C9 *2/*2 Poor Metabolizer)

Consider starting at half the lowest recommended dose and evaluate response the first week. Be alert to gastrointestinal adverse events. Consider alternative medication for the management of Juvenile Rheumatoid Arthritis.

Citalopram (Celexa) Evidence Level: 1

Increased Sensitivity to Citalopram (CYP2C19 *7/*7 Poor Metabolizer)

Consider using citalopram at lower doses and monitor the patient for side effects. Dose escalations over 20 mg/day for CYP2C19 poor metabolizers are not recommended.

Clobazam (Onfi) Evidence Level: 1

Increased Sensitivity to Clobazam (CYP2C19 *7/*7 Poor Metabolizer)

IIn CYP2C19 Poor metabolizers, plasma levels of the active metabolite N-desmethylclobazam were 5-fold higher than those found in CYP2C19 normal metabolizers. Therefore, the starting dose should be 5 mg/day and dose titration should proceed slowly according to weight. Patients should be titrated initially to 10 mg /day (≤30 kg body weight) or 20 mg/day (>30 kg body weight). If necessary and based upon clinical response, an additional titration to the maximum doses 20 mg/day (≤30 kg body weight) or 40 mg/day (>30 kg body weight) may be started on day 21.

Clomipramine (Anafranil) Evidence Level: 1

Increased Sensitivity to Clomipramine (CYP2C19 *7/*7 Poor Metabolizer)

Consider a 50% reduction of recommended clomipramine starting dose and monitor the plasma concentrations of clomipramine and desmethyl-clomipramine to adjust the dose.

Clopidogrel (Plavix) Evidence Level: 2

Significantly Reduced Response to Clopidogrel (CYP2C19 *7/*7 Poor Metabolizer)

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Patient Reference

PATIENT CARD: CUT OUT AND CARRY IN YOUR WALLET

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Pharmacogenetic Test Results

Patient: John Doe DOB 1/1/1962

CYP2C19	*7/*7	Poor Metabolizer
CYP2C9	*2/*2	Poor Metabolizer
CYP2D6	*1/*1	Normal Metabolizer
CYP3A4	*3/*3	Intermediate Metabolizer
CYP3A5	*3C/*3C	Poor Metabolizer

APOE	ε3/ε4	Increased Risk of Hyperlipidemia/Atherosclerotic Vascular Disease
Factor II Factor V Leiden	20210G>A GA 1691G>A GG	Increased Risk of Thrombosis
MTHFR	677C>T CC 1298A>C AA	No Increased Risk of Hyperhomocysteinemia
VKORC1	-1639G>A G/A	Intermediate Warfarin Sensitivity

Advantages of MD GeneticPro®

Personalized Medicine to Improve & Save Lives

Results

Help predict patients' response to medications.

Assist in clarifying patients' lower than expected clinical response.

Explains patients' higher than expected incidence of adverse effects.

Insights

Manage treatment strategy to maximize safety and efficacy.

Clarify or validate a patient's UDT results.

Individualized Therapy

- **More refined diagnostic testing to enhance patient outcomes.**
- **Identify treatment and dosing options most likely to result in improved quality of life.**
- **Avoid adverse drug reactions.**

Convenience

Patient-friendly saliva or blood-based testing.

Informative and easy-to-read reports.

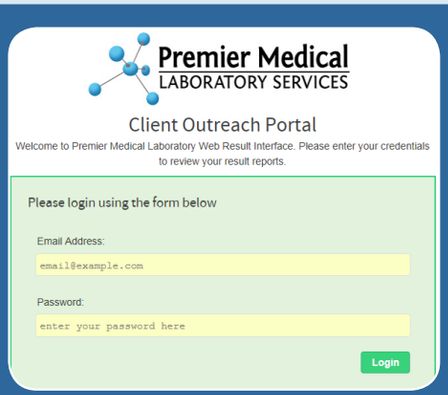
Assists in informed decision making.

MD GeneticPro® improves clinical outcomes and increases patient safety.

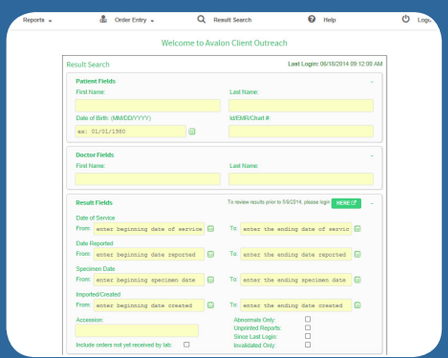
HIPAA Compliant Web Portal Results

Convenient Online Reporting

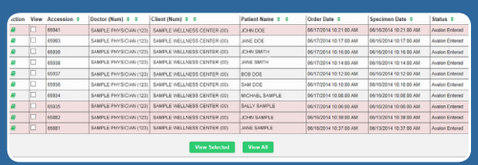
Our HIPAA Compliant web portal is private, secure and easy for you and your staff to use. Whether you keep physical records, have a paperless office, or have an integrated Electronic Medical Record (EMR) system, our reporting system can seamlessly integrate with your practice.



Secure Login — Private and HIPAA Compliant



Convenient Search — Search by Patient Name or Date of Service, and choose to see only Abnormal results, Unprinted results, or all reports since your last login.



At-A-Glance Results — Results are easy to view at a glance. Abnormal reports are highlighted in red, normal in gray. A flag alerts you to results already printed. Choose to view individual reports, or several at once.

Integrated Reports — Easily save or print PDF reports, or automatically download to your EMR system.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