YOUR CODE FOR PERSONALIZED MEDICINE

THE NEW STANDARD OF CARE
Genetic testing makes it possible to know a priori how your patients will metabolize a specific drug. Approximately 50% of the population have genetic variations that can increase or decrease the availability of cytochrome enzymes that are essential for proper drug metabolism and conversion. The comprehensive genetics4you™ genotyping panel can assess up to five (5) of the most influential CYP450 enzymes — 2C19, 2C9 (and VKORC1), 2D6, 3A4 and 3A5 and detect over 50 variants known to affect drug metabolism, and 3 other genes with well documented variants — Factor II, Factor V Leiden and Mthfr, which are useful to identify inherited risk factors related to prothrombin deficiency, hyperhomocysteinemia and thrombosis.

WHY PERFORM GENETIC TESTING?
Clinical studies have reported that high percentages of patients being treated for cardiac disease, pain management, psychiatric disorders, gastric ulcers or reflux, and diabetes carry genetic variants that alter the rate they will metabolize or activate many commonly prescribed drugs, preventing patients from either getting the intended therapeutic response from a given drug. Patients with gene variants are eight times more likely to experience an adverse drug reaction or lack of efficacy to their prescribed medication.

Genetic testing benefits the doctor, the patient—and the healthcare system by delivering better outcomes and potential savings by treating patients with the right drug the first time and by reducing the number of potentially serious adverse reactions.

“EVERYONE HAS A UNIQUE GENETIC ‘SIGNATURE’ — THAT MAKES THEM RESPOND DIFFERENTLY TO DRUGS.”

A physician reviews the molecular diagnostic cardiac panel genotyping results with a patient and prescribes a "tailored" treatment plan based on their unique “genetic signature.”
The comprehensive genotyping test panel is typically performed on a person once in their lifetime to determine a patient’s unique ‘genetic blueprint’, which can be used by their physician(s), over and over, as an important reference tool for choosing the most effective prescriptions or drug therapies, that produce the best clinical outcomes—for every patient. With the average Medicare patient seeing more than 6 physicians annually, and those with chronic diseases seeing over 10 physicians, choosing and managing a patient’s drug therapies and avoiding adverse drug-drug interactions is becoming increasingly important to optimizing overall patient care and outcomes.

There are two primary types of genetic tests available to patients, Molecular diagnostic testing identifies inherited genetic variants that predispose a patient to certain diseases; and pharmacogenomic testing, which identifies a multitude of genetic biomarkers or variants that determine an individual’s specific response to a broad array of drugs used to treat cardiac disease (Plavix®, Coumadin®, beta blockers, antiarrhythmics, CA channel blockers and statins), neuropsychiatric disorders (antidepressants, anti-seizure, and migraines), gastric ulcers or reflux (PPI’s), diabetes (sulfonylureas), and pain management (opioids, NSAIDs, and benzodiazepines).

The value of knowing your patient’s ‘genetic blueprint’ will enhance your ability to prescribe the most effective treatments for individual patients; determine proper dosages of drugs based on predetermined patient-specific metabolic or inherited biomarkers; avoid serious drug-drug interactions and reduce the possibility of using drugs or dosages that could result in catastrophic adverse effects. A single genetics4you™ genotyping test once in a lifetime—that’s all it takes to introduce personalized medicine to your patients—and begin practicing the New Standard of Care.

The FDA informs healthcare providers that it is known that certain patients may not properly metabolize certain drugs and convert it to its’ active form. The FDA indicates that genetic testing can identify differences in patients’ with reduced CYP2C19 function. Numerous clinical studies also demonstrate that CYP2C9, CYP2D6 or CYP3A4/3A5 variants can reduce metabolic function. Approximately 120 drugs now have the FDA Black Box Labeling. These genetic tests are covered Medicare, MediCAL and most major insurance carriers.
**CYP450 2C19 Genotyping Test**

**Clinical Relevance:** Approximately 25% of all outpatient prescription drugs filled in the US are taken by patients with genetic polymorphisms that affect absorption, metabolism or excretion. The CYP2C19 enzyme metabolizes ~15% of all drugs. CYP2C19 is a primary metabolic enzyme for clopidogrel, proton pump inhibitors (PPI’s), antidepressants and certain pain medications. Plavix (clopidogrel) is the world’s second best selling drug. Genetic variation that impairs metabolism is seen in 30% of Caucasians, 40% of African Americans and 55% of East Asians. Studies indicate that carriers of a reduced function allele for CYP2C19 have a 3.58X greater risk for major adverse CV events and a 53% relative higher risk of death over 15 months due to CV causes, MI or stroke. Stent patients have a threefold increased risk of stent thrombosis.


**CYP450 3A4/3A5 Genotyping Test**

**Clinical Relevance:** CYP3A4 and 3A5 metabolize up to 50% of all clinical drugs, including statins, calcium channel blockers, benzodiazepines, antipsychotics, opioids, antidepressants, acetaminophen and chemotherapeutics. The FDA recommends 3A4/3A5 genetic testing prior to initiating or reinitiating treatment with Ticagrelor (Brilinta) or Fluvoxamine. 3A4/3A5 metabolic abnormalities exist in ~1 of 100 patients.


**Factor II/V/MTHFR Genotyping Test**

**Clinical Relevance:** The Factor V Leiden mutation is the most common variant associated with inherited thrombosis. Its prevalence is ~4-6% in the general US population, and accounts for 85-95% of activated protein C resistant cases. The Factor II (Prothrombin variant gene is the second most common genetic defect for inherited thrombosis and is present in 1-2% of the general population. Hyperhomocysteinemia is a risk factor for coronary artery disease, venous thrombosis and stroke. Methylenetetrahydrofolate reductase (MTHFR) is a key enzyme in the metabolism of homocysteine.

**Genetic Variants:** FV G1691A, FII G20210A, MTHFR A1298C and C677T alleles.

**CYP450 2C9/VKORC1 Genotyping Test**

**Clinical Relevance:** CYP2C9 is a primary metabolic enzyme for warfarin, NSAIDs and sulfonylurea medications. Warfarin is the most widely prescribed anticoagulant for the prevention and treatment of thromboembolic events. The active metabolizer of warfarin is CYP2C9. Other polymorphisms in the CYP2C9 gene are associated with decreased warfarin clearance and increased risk of bleeding. Major bleeding occurred during the first 90 days after treatment in 50% of patients. Another polymorphism is the VKORC1 gene which is associated with warfarin sensitivity and decreased maintenance dose requirements of the medication. Complications of warfarin therapy account for over 10% of hospital admissions and 15% of all severe drug-induced adverse events. Studies indicate that the routine incorporation of genetic testing into warfarin therapy protocols significantly ease both the health and financial risks currently associated with treatment.

**Genetic Variants:** CYP450 2C9 *2, *3, *4, *5, *6 and *11, and VKORC1 3673 (-1639G>A), 6009(698C>T), 6484 (1173C>T), 6853 (1542G>T), 7566 (2255C>T), 8773 (358C>T), 9041 (3730G>A) and 5808 (497T>C) alleles.

**CYP450 2D6 Genotyping Test**

**Clinical Relevance:** CYP2D6 metabolizes more than 25% of all drugs, including tamoxifen, many antidepressants, antipsychotics, beta-blockers and opioids. This assay detects variants of the CYP2D6 gene in patients that cause altered enzymatic activity that increase the risk of adverse drug reactions or therapeutic failure to standard dosages of CYP2D6 substrates. Medications requiring activation or inactivation by CYP2D6 should be used with caution in patients with these variants. Patients are categorized as extensive or normal metabolizers (EM), Intermediate metabolizers (IM), poor metabolizers (PM), or ultra-extensive metabolizers (UM). Indicated for use in determining strategy and treatment doses for therapeutics that are metabolized by the CYP2D6 gene product. If co-administered with a CYP2D6 inhibitor, blood levels and effect of the beta blocker may increase resulting in bradycardia, hypotension or heart failure with the highest risk in extensive and/or poor metabolizers (EM).

MOLECULAR DIAGNOSTICS ARE THE TOOLS OF MODERN MEDICINE.
THE NEW STANDARD OF CARE FOR CARDIOLOGY
‘PERSONALIZED MEDICINE’

Modern genetic molecular diagnostics and pharmacogenomic testing introduces a new Standard of Care for physicians and their patients. ‘Personalized Medicine’ ensures that every patient receives the most effective treatment and care based on individual genetic biomarkers that determine an individual’s inherent ability to respond to a particular drug or therapy.

CLINICAL REFERENCES

1 American College of Clinical Pharmacology. Pharmacogenomics: Application to Patient Care. AACP; Kansas City, Mo: ACCP; 2004: 262, 263, 290
2 FDA Drug Safety Communication: Reduced Effectiveness of Plavix (clopidogrel) in Patients Who Are Poor Metabolizers of the Drug; http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncement/ucm204253.htm
8 Prothrombin (G20210A) Gene Polymorphism (PTG G20210A); http://pathology.mc.duke.edu/coag/PTGflyer2.html.