

# **APPLIED GENETICS CARDIAC PANEL**

***“Decreasing Adverse Events, Improving Outcomes, and Lowering Systemic Costs”***

## **CYP 2C9/VKORC-1**

Cytochrome P450 2C9 is responsible for metabolizing warfarin. CYP2C9 is a highly polymorphic liver enzyme of the cytochrome P450 super family involved with the metabolism and elimination of many commonly prescribed drugs. Genetic polymorphisms in CYP2C9 are common and can affect therapeutic response to drugs. The enzyme activity is expressed at highly variable levels. Three phenotypes are identified: poor metabolizers (**PM-no active alleles**), intermediate metabolizers (**IM-one inactive allele**) and normal metabolizers (**NM-two normal alleles**).

### **CLINICAL SIGNIFICANCE**

CYP2C9 phenotype prevalence is 2-4% Poor Metabolizer, >35% Intermediate Metabolizer for CYP2C9. Drugs metabolized by this enzyme approximately 15%.

Cytochrome P-240 2C9 Mutations Detected		
CYP2C9 allele	Nucleotide change	Effect on Enzyme Metabolism
*1	None (wildtype)	Normal
*2	430C>T	Decreased
*3	1075A>C	Decreased
*4	1076T>C	Decreased
*5	1080C>G	Decreased
*6	818delA	None
*8	449G>A	Decreased
*11	1003C>T	Decreased

#### **1. FDA APPROVES UPDATED WARFARIN (COUMADIN) PRESCRIBING INFORMATION NEW GENETIC INFORMATION MAY HELP PROVIDERS IMPROVE INITIAL DOSING ESTIMATES OF THE ANTICOAGULANT FOR INDIVIDUAL PATIENTS**

The U.S. Food and Drug Administration announced today the approval of updated labeling for the widely used blood-thinning drug, Coumadin, to explain that people's genetic makeup may influence how they respond to the drug.

#### **2. <http://content.onlinejacc.org/cgi/content/full/j.jacc.2010.03.009v1>**

*“In this comparative effectiveness study, which encompassed thousands of outpatients in practice settings across the country, we found significant reductions in adverse events for patients who were genotyped early in the course of warfarin treatment. Compared with historical controls, genotyped patients had 31% fewer all-cause hospitalizations and 28% fewer hospitalizations for bleeding or thromboembolism. Our findings suggest that the addition of genotyping to usual care reduces the risk of hospitalization by approximately 30% among patients initiating warfarin. This reduction is consistent with a meta-analysis conducted by Eckman et al. (17), which found a trend toward a 32% reduction in major bleeding across 3 randomized trials.”*

3. <http://www.mayomedicallaboratories.com/mediax/articles/communique/2008/mc2831-0808.pdf>

In 2006, McWilliam et al from the AEI Brookings Join Center for Regulatory Studies published a working paper that summarizes research from available adverse event data for warfarin and the estimated cost of those ADEs. The paper estimates the health benefits and reduction in health care costs if patients undergo genetic testing. The authors believe that the results of the FDA Critical Path Initiative will show that implementing **genetic testing can reduce health care costs for warfarin-related ADEs by \$1.1 billion annually**. Estimated hospitalization costs for either a **bleeding or a clotting ADE are \$18,000 to \$25,000 for each patient**. For those **patients who suffer strokes while taking warfarin, estimated costs for hospitalization and medical care are ~\$40,000 per patient**. If 2 million patients start warfarin each year, and an estimated 22 % are hospitalized for ADEs, the overall health care costs can be astounding. McWilliam et al surmise that **with genetic testing followed by appropriate dosing, the risk of stroke could be reduced 50%** and costs could be reduced significantly.

4. *CYP2C9 Genotype guided Warfarin Prescribing Enhances the Efficacy and Safety of Anticoagulation: A prospective Randomized Controlled Study*. Caraco et. al, Nature 03/08

- The first therapeutic INR was reached 2.73 days earlier in PGx dosing group
- Stable anticoagulation reached 18.1 days earlier
- PGx group spent more time within INR range
- PGx group experienced less bleeding events (3.2%, whereas the standard group had 12.5%)
- CYP2C9 genotype guided warfarin therapy is more efficient and safer than the average dose protocol

5. **Key Points:**

Major bleeding occurs in the first **90 days of treatment in 50% of patients**

**Fatal hemorrhages** have been reported as high as 1.1%

Adverse events from warfarin account for **15% of all severe adverse events**

The **2C9 sample reports** shows the dosing algorithm.

## **CYP 2C19**

Cytochrome P450 2C19 is responsible for metabolizing clopidogrel. CYP2C19 (cytochrome P450 2C19) acts on 5-10 % of drugs in current clinical use. About 2-6% of individuals of European origin, 15-20% of Japanese, and 10-20% of Africans have a slow acting, poor metabolizer (**PM**) form of this enzyme. However there is wide variability among populations. For example, the percent of Polynesians who are poor metabolizers ranges from 38-79% depending on location. Five phenotypes are identified: poor metabolizers (**PM-no active alleles**), intermediate metabolizers (**IM-one inactive allele**), normal metabolizers (**NM-two normal alleles**), extensive metabolizers (**EM-one normal and one gain of function allele**), and ultra-rapid metabolizers (**URM-two gain of function alleles**).

### **CLINICAL SIGNIFICANCE**

PM phenotype prevalence is 2-6% PM Caucasian, 13-19% PM Asians, 10-20% PM African, 24-36% IM, ~5% URM;

Drugs metabolized by this enzyme approximately 5-10%.

Cytochrome P-450 2C19 Mutations Detected		
CYP2C19 allele	Nucleotide change	Effect on Enzyme Metabolism
*1	None (wildtype)	Normal
*2	19154G>A	Decreased
*3	17948G>A	Decreased
*4	1A>C	Decreased
*6	13748G>A	Decreased
*7	19294T>A	Decreased
*8	12711T>C	Decreased
*9	12784G>A	Decreased
*10	19153C>T	Decreased
*17	-806C>T	Increased

1. <http://www.medscape.com/viewarticle/439805>  
Stent thrombosis is a costly business. Substantial resources are already spent in prevention; on stents, which have reduced the incidence of both acute and subacute closure, and **anticoagulation regimens, which have become more effective but are more expensive**. Reynolds et al. estimated the cost of treating a patient with **subacute thrombosis to be ~ \$11,000**, a figure not dissimilar to that of the treatment of acute myocardial infarction with primary PCI.
2. <http://www.cathlabdigest.com/articles/Subacute-Stent-Thrombosis-Case-Presentation-and-Brief-Review>  
**Estimated direct hospital costs for this patient were \$13,250, including \$7200** from her catheterization laboratory procedure.
3. On March 12, 2010 the US Food and Drug Administration (FDA) announced it is requiring a **boxed warning** for clopidogrel (*Plavix*, Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership) to caution that (especially the) **poor metabolizers of the drug may not receive full protection from myocardial infarction, stroke, and cardiovascular death**. Poor *CYP2C19* metabolizer status is linked to a decreased antiplatelet response to clopidogrel and occurs in **4% of the general population, varying from 2% to 14% by race**. Poor metabolizers of clopidogrel may not achieve appropriate levels of the active metabolite, thereby decreasing their protection from **myocardial infarction, stroke, and cardiovascular death**.
4. *CYP2C19*\*17 carrier status is significantly associated with enhanced response to clopidogrel and an increased risk of bleeding. (*Circulation*. 2010;**121:512-518**.) Of 1524 patients, 22.9% possessed the \*17 variant. 2 patients had fatal bleeds (1-wt/\*17, 2-\*17/\*17). “*For the individual patient undergoing coronary stent placement, the information provided by genetic and platelet function testing may be complementary in improving patients’ outcomes.*”

5. **Dosing:**

**NM**-300mg loading dose continued with 75mg daily maintenance dose.

**N-IM**-300mg loading dose continued with 75mg daily maintenance dose. If the effect of the maintenance dose is not sufficient, consider using a larger daily maintenance dose. (150mg)

**IM**-300mg loading dose continued with 75mg daily maintenance dose. If the effect of the maintenance dose is not sufficient, consider using a larger daily maintenance dose. (150mg)

**PM**-600mg loading dose continued with 150mg daily maintenance dose. Other drugs should be considered. Close monitoring is advised.

**RM**-300mg loading dose continued with 75mg daily maintenance dose. Daily doses could be lowered. Close monitoring is advised. RM may be at a higher bleeding risk. Other drugs should be considered.

**URM**-Consider starting clopidogrel at a lower loading dose and a lower maintenance daily dose. Consider using other drugs. Close monitoring is advised. URM may be at increased bleed risk.

*emedicine.medscape.com/article/1733280-overview*

*JACC :CARDIOVASCULAR INTERVENTIONS, VOL , NO.1, 2009 NOVEMBER 2009: 1095-101*

**CYP 2D6**

Cytochrome P450 2D6 is responsible for metabolizing beta-blockers. 2D6 acts on one-fourth of all prescription drugs, including the selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants (TCA), beta-blockers such as Inderal and the Type 1A antiarrhythmics. Approximately 10% of the population has a slow acting form of this enzyme and 7% a super-fast acting form. Thirty-five percent are carriers of a non-functional 2D6 allele, especially elevating the risk of ADRs when these individuals are taking multiple drugs. Four phenotypes are identified: poor metabolizers (**PM-two non function alleles**), intermediate metabolizers (**IM-one inactive allele, or two reduced function alleles**), normal metabolizers (**NM-at least one functional allele**), rapid metabolizers (**RM-multiple functional copies of a single CYP2D6 gene**).

**CLINICAL SIGNIFICANCE**

Phenotype prevalence is approximately 10 % PM, 7% UM, and 35% IM.

Drugs metabolized by this enzyme - approximately 25%.

Cytochrome P-450 2D6 Mutations Detected		
CYP2D6 allele	Variant	Effect on Enzyme Metabolism
*1	None (wild type)	Normal
*2	2850C>T	Normal
*3	2549A>del	Inactive
*4	1846G>A	Inactive

*5	Gene Deletion	Inactive
*6	1707T>del	Inactive
*7	2935A>C	Inactive
*8	1758G>T	Inactive
*9	2615_2617 delA AG	Partially active
*10	100C>T	Partially active
*12	124G>A	Inactive
*14	1758G>A	Inactive
*17	1023C>A	Partially active
*29	1659G>A	Partially active
*41	2988G>A	Partially active
*XN	Gene Duplication *1,*2,*4,*10,*41	Increased Activity

Metabolizer Status	Caucasian	African American	Asian
Normal	70%	40%	50%
Poor	5%	30%	45%
Non	7-10%	15-20%	1%
Rapid	5-15%	2-20%	2%

**Key Point:**

Detecting genetic variations in drug-metabolizing enzymes is useful for identifying individuals who may experience adverse drug reactions with conventional doses of certain medications. Individuals who possess CYP2D6 poor metabolizer variants may exhibit different pharmacokinetics (drug levels) than normal individuals. As a result, such individuals may require non-conventional doses of medications that require CYP2D6 activity for biotransformation. Conversely, medications that do not require CYP2D6 biotransformation may be preferentially selected for patients with potentially impaired CYP2D6 metabolic capacity to avoid adverse drug reactions.

1. <http://www.ncbi.nlm.nih.gov/m/pubmed/19817501/>
2. <http://www.ncbi.nlm.nih.gov/m/pubmed/19902987/?i=2&from=/19817501/related>
3. <http://www.ncbi.nlm.nih.gov/m/pubmed/19902987/?i=2&from=/19817501/related>

These articles discuss 2D6 genotyping and significance of metabolizer status.

PMs are likely to exhibit therapeutic failure, and ultrarapid metabolizers (UMs) are likely to experience adverse effects and toxicities

## **ApoE**

CVD- ApoE is reported to increase an individual carrier's differential susceptibility to CAD events. A carrier's genotype can help a clinician better treat their patients. For example, subjects with the e4 allele are typically poor responders to lipid lowering drugs, except for probucol and simvastatin.

Brain/Consussion- ApoE is thought to be responsible for the transportation of lipids within the brain and maintaining the structural integrity of the microtubule within the neuron. There are 3 ApoE genotypes - ApoE2(12%) (e2/e2), ApoE3 (63%) (e3/e2 and e2/e4,) and ApoE4 (25%) (e4/e3 and e4/e4)

People with ApoE e2/e2 alleles are at a higher risk of premature vascular disease, but they may never develop disease. Likewise, they may have the disease and not have e2/e2 alleles because it is only one of the factors involved. ApoE genotyping adds additional information and, if symptoms are present, e2/e2 can help confirm type III hyperlipoproteinemia.

Those who have ApoE e4/e4 are more likely to have atherosclerosis. People who have symptoms of late onset Alzheimer's disease (AD) AND have one or more ApoE e4 copies of the e4 gene are more likely to have AD. However, it is not diagnostic of AD and should NOT be used to screen asymptomatic people or their family members. Many of those who have e4 alleles will never develop AD. Even in symptomatic people, only about 60% of those with late onset AD will have ApoE e4 alleles.

ApoE e3 has "normal" lipid metabolism, thus may not have any genotype impact.

**The AHA's Dietary Guidelines (revision 200)** specifically references **the need to consider how underlying genetic** and metabolic heterogeneity may limit the potential for generalized nutritional guidelines to address individual dietary responsiveness. See chart.

**FIGURE 1  
APO E GENOTYPE CORRELATION TO TREATMENT RESPONSE**

		Apo E2		Apo E3		Apo E4	
Genotype		2/2	2/3	3/3	2/4	3/4	4/4
Population Frequency		1%	10%	62%	2%	20%	5%
Dietary Contribution	<b>Soluble Fiber</b> <sup>1</sup>	↓ LDL		↓ LDL		↓ LDL	
	<b>Fish Oil</b> <sup>2</sup>	↓↓ TG ↓ small dense LDL ↑ HDL		↓ TG ↓ small dense LDL ↑ HDL		↓ TG ↓↓ small dense LDL ↓ HDL may ↑ LDL	
	<b>Plant Sterols</b> <sup>3</sup>	↓ LDL ↓ Apo B		↓ LDL ↓ Apo B		↓ LDL ↓ Apo B	
	<b>Soy Protein</b> <sup>4</sup>	↓ Apo B		↓ Apo B		↓ Apo B	
Dietary Fat and Alcohol Effects	<b>Low Fat Diet</b> <sup>5,6</sup>	↓ LDL ↑ small dense LDL		↓↓ LDL ↔ small dense LDL		↓↓↓ LDL ↓ small dense LDL	
	<b>Moderate Fat Diet</b> <sup>6</sup>	↔ LDL ↔ small dense LDL		↓ LDL ↓ small dense LDL		↓ LDL ↑↑ small dense LDL	
	<b>Moderate Alcohol</b> <sup>7</sup>	↑ HDL ↓ LDL		↑ HDL		↓ HDL ↑ LDL	

**Legend:** ↓ decreases    ↑ increases    ↔ no change    ↓↓ significantly decreases    ↑↑ significantly increases

- References:** 1. a) Am J Clin Nutr. 1997 Sep;66(3):584-90 b) Metabolism 1993(42):585-93  
 2. Arterioscler Thromb Vasc Biol. 2000 Aug;20(8):1990-7  
 3. Nutrition 2002 Jul-Aug;18(7-8):561-5  
 4. Nutr Metab Cardiovasc Dis 2000 Dec;10(6):315-22  
 5. Am J Clin Nutr 2003;77:1098-111  
 6. J. Nutr 2004 134: 25 17-2522  
 7. a) Am J Clin Nutr. 2001 Apr;73(4):736-45 b) Obes Res 2003 Oct;11(10):200-6  
 c) Atherosclerosis 2004 Mar;173(1):79-87 d) J Neural Trans 2003 Apr;110(4):401-11  
 e) Proc Nutr Soc 2004(63):5-10 f) Arterioscler Thromb Vasc Biol. 2002 May 1;22(5):824-31

† This chart represents a summary of reported metabolic responses seen with different Apo E genotypes. Providers must consider the appropriate context for each patient's best therapeutic recommendation, based on their overall metabolic and cardiac risk profile.

1. <http://ghr.nlm.nih.gov/gene/APOE>
2. Read the Berkeley Heart White paper in the DropBox.

**Factor II**

- Factor I, Prothrombin, is a clotting protein that functions in the clotting cascade.
- Genetically, there is an amino acid substitution on the 3' untranslated region which causes an increase in mRNA translation subsequently increasing protein expression.
- The prevalence is 2% in whites, with descendants of Southern Europeans having an increased prevalence. This mutation is rarely seen in Asians and Africans.
- This mutation causes a 2 to 3 fold risk in developing venous thrombosis.

**Factor V**

- Factor V, Leiden, mutation causes anti-clotting proteins (aPC-activated protein C) from breaking down factor V in the blood, therefore causing an increase in clotting risk.
- Arginine 506 is substituted with a Glutamine.

- There is a 4 to 8 fold increase in clotting adverse events in heterozygotes and 50 to 100 fold increases in homozygotes. Contraceptives cause a 30 fold increase in such adverse events.

**Compliance:**

1. <http://www.rxfacts.org/professionals/antiplatelet.php>
  - The cost of clopidogrel (Plavix), dipyridamole-aspirin (Aggrenox), and prasugrel (Effient) are more than 100 times that of aspirin. Despite this, it can still be economically reasonable to prescribe these drugs in appropriately chosen patients. For example, one economic analysis found that clopidogrel (Plavix) used alone in patients with peripheral vascular disease appears to be highly cost-effective.<sup>9</sup>
  - *Differences in cost may be particularly relevant when choosing between agents that are equally effective or equally safe. This is especially important in patients for whom an unaffordable drug will result in non-compliance.*

**Cost:**

- The prevalence of Potentially Inappropriate Medications in the elderly ranges from 12 to 40%, and PIMs lead to greater odds of hospitalization and death.
 

*Lau DT et al. Arch Intern Med 2005;165:68-74*
- 1994: \$73 bln on meds; \$76 bln on DRPs
 

*A cost of illness model Arch Intern Med 1995;155(18):1949-56*
- 1997: In nursing homes, every \$1 on meds; \$1.3 on cleaning up DRPs
 

*Healthcare cost of drug-related morbidity. Arch Intern Med 1997;157(18):2089-96*
- 2001: \$133 bln on meds; \$174 bln on DRPs
 

*J Am Pharm Assoc 2001;41(2):192-97*
- ADEs and their subsequent injuries lead to increased hospital costs. Depending on facility size, hospital costs annually for all ADEs are estimated to be as much as \$5.6 million per hospital.
 

Bates DW, Spell N, Cullen DJ, et al. The costs of adverse drug events in hospitalized patients. *JAMA 1997;277(4):307-11*

Bates DW, Cullen DJ, Laird N, et al. Incidence of adverse drug events and potential adverse drug events. *JAMA 1995;274(1):29-34*