DetoxiGenomic™ Profile

Physician's Copy

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DOB: January 26, 1952
Sex: F
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Order Number: F6270034
Completed: January 04, 2013
Received: December 27, 2012
Collected: December 26, 2012

Security Code: 7059323

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PHASE I Detoxification: The First Line of Defense

In Phase I detoxification, enzymes, known collectively as the cytochrome P-450 system, use oxygen to modify toxic compounds, drugs, or steroid hormones. Many toxins must undergo Phase II detoxification after a reactive site has been formed. Because there are many different toxic compounds the body might encounter, there are many variants of Phase I enzymes.

(CYP1A1) detoxifies polycyclic aromatic hydrocarbons (PAHs) produced from the combustion of organic materials (exhaust fumes, charbroiled meats, etc.).

(CYP1B1) is involved in the 4-hydroxylation of estrogen.

(CYP2A6) detoxifies nitrosamines and nicotine

(CYP2C9) detoxifies coumadin® and sulfonylureas.

(CYP2C19) detoxifies proton-pump inhibitors (e.g., prilosec®) and many anticonvulsants (e.g., valium®).

(CYP2D6) detoxifies ~20% of all prescription drugs including tricyclics, MAOIs, SSRIs, opiates, anti-arrhythmics, beta-blockers, Cimetidine, etc.

(CYP2E1) detoxifies nitrosamines and ethanol (acetaldehyde).

(CYP3A4) detoxifies over 50% of all prescription medications and most steroid hormones.

Cytochrome P-450		
Result	Gene	internet information
✔	**CYP1A1** *	www.genovations.com/gdgen01
●	**CYP1B1** *	www.genovations.com/gdgen02
✔	**CYP2A6**	www.genovations.com/gdgen10
●	**CYP2C9** *	www.genovations.com/gdgen05
✔	**CYP2C19** *	www.genovations.com/gdgen06
✔	**CYP2D6**	www.genovations.com/gdgen03
✔	**CYP2E1**	www.genovations.com/gdgen04
●	**CYP3A4** *	www.genovations.com/gdgen07

Use of H2 blockers (e.g. Cimetidine) should be avoided as these bind to the heme-containing reactive site of all CYPs inhibiting binding to toxins.

Your Results: Polymorphisms (SNPs) in the genes coding for a particular enzyme can increase or, more commonly, decrease the activity of that enzyme. Both increased and decreased activity may be harmful. Increased phase I clearance without increased clearance in Phase II can lead to the formation of toxic intermediates that may be more toxic than the original toxin. Decreased Phase I clearance will cause toxic accumulation in the body. Adverse reactions to drugs are often due to a decreased capacity for clearing them from the system.

General Therapies to Improve Detoxification:

Foods that generally improve Phase I detoxification and as well improve the efficiency of Phase II conjugation are generally recommended for individuals with CYP SNPs. These include most vegetables and fruits, but especially cruciferous vegetables (broccoli, Brussels sprouts, cauliflower, watercress, and cabbage), garlic, onions, soy, grapes, berries, green and black tea, and many herbs and spices like rosemary, basil, turmeric, cumin, poppy seeds, and black pepper. Indeed, improving Phase I and Phase II detoxification helps explain why vegetables and fruits protect against many cancers.

Key		
	✔	Optimal genomic potential - no polymorphism detected
	●	Polymorphism detected in this enzyme, increasing your susceptibility to toxins, if exposed
	*	Multiple SNP locations were evaluated for these genes
	NR	See commentary if applicable

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Improving Healthcare for Chronic Disease

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PHASE II Detoxification: Conjugation of Toxins and Elimination

In Phase II detoxification, large water-soluble molecules are added to toxins, usually at the reactive site formed by Phase I reactions. After Phase II modifications, the body is able to eliminate the transformed toxins in the urine or the feces (through the bile).

(COMT SNP) higher risk for depression, bipolar disorder, ADHD and alcoholism.

Methylation

Result	Gene	SNP Location	Internet Information	Affects
++	**COMT**	V158M	www.genovations.com/gdv158m	Liver/Gut

Your Results: Catechol-O-methyl transferase is the enzyme primarily responsible for breaking down the neurotransmitters dopamine, epinephrine, and norepinephrine.

(NAT SNP) both slow and rapid acetylators are at increased risk for developing lung, colon, bladder, or head & neck cancer.

Acetylation (N-acetyltransferase)

SLOW METABOLIZER POLYMORPHISM

Result	Gene	SNP Location	Internet Information	Affects
−−	**NAT1**	R64W	www.genovations.com/gdr64w	All Cells
−−	**NAT1**	R187Q	www.genovations.com/gdr187q	Liver/Gut
+−	**NAT2**	I114T	www.genovations.com/gdi114t	Liver/Gut
+−	**NAT2**	R197Q	www.genovations.com/gdr197q	Liver/Gut
−−	**NAT2**	G286E	www.genovations.com/gdg286e	Liver/Gut
−−	**NAT2**	R64Q	www.genovations.com/gdr64q	Liver/Gut

FAST METABOLIZER POLYMORPHISM

+−	**NAT2**	K268R	www.genovations.com/gdk268r	Liver/Gut

Your Results: N-acetyl Transferase detoxifies many environmental toxins, including tobacco smoke and exhaust fumes. Polymorphisms can result in slower than normal or faster than normal addition of an acetyl group to these toxins. Slow acetylators have a build up of toxins in the system and rapid acetylators add acetyl groups so rapidly that they make mistakes in the process. Both slow and rapid acetylators are at increased risk for toxic overload if they are exposed to environmental toxins. If the toxin exposure is reduced, the risk is reduced.

(GST SNP) The GST isoforms (M1, P1, and T1) are more or less prevalent in various tissues; all catalyze the conjugation of electrophilic compounds with glutathione. Defects in GST activity can contribute to fatigue syndromes, and to various cancers throughout the body.

Glutathione Conjugation (Glutathione s-transferase)

Result	Gene	Location	Internet Information	Affects
ABSENT	**GSTM1**	1p13.3	www.genovations.com/gdrgstm1	Liver/Kidney
+−	**GSTP1**	I105V	www.genovations.com/gdrgstp1	Brain/Skin
−−	**GSTP1**	A114V	www.genovations.com/gda114v	Brain/Skin

Your Results:
Glutathione-S-transferase detoxifies many water-soluble environmental toxins, including many solvents, herbicides, fungicides, lipid peroxides, and heavy metals (e.g., mercury, cadmium, and lead). The various forms of GST work together to eliminate toxins. Decreased glutathione conjugation capacity may increase toxic burden and increase oxidative stress.

(SOD SNP) SOD1 is present in the cytosol; SOD2 is present in the mitochondria. Changes in the SOD enzyme are associated with changes in risk for neurodegenerative disorders like ALS.

Oxidative Protection

Result	Gene	SNP Location	Internet Information	Affects
−−	**SOD1**	G93A	www.genovations.com/gdg93a	Cytosol
−−	**SOD1**	A4V	www.genovations.com/gda4v	Cytosol
+−	**SOD2**	A16V	www.genovations.com/gda16v	Mitochondria

Your Results: Superoxide Dismutase is an enzyme that protects cells from increased oxidative stress and free radical damage to cell structures like membranes, mitochondria, DNA, and proteins.

Key

−−	Neither chromosome carries the genetic variation.	Homozygous negative or wild type
+−	One chromosome (of two) carries the genetic variation.	Heterozygous positive
++	Both chromosomes carry the genetic variation.	Homozygous positive

(You inherit one chromosome from each parent)

This test has been developed and its performance characteristics determined by Genova Diagnostics, Inc. It has not been cleared or approved by the U.S. Food and Drug Administration.

Commentary is provided to the practitioner for educational purposes, and should not be interpreted as diagnostic or treatment recommendations. Diagnosis and treatment decisions are the responsibility of the practitioner.

The accuracy of genetic testing is not 100%. Results of genetic tests should be taken in the context of clinical representation and familial risk. The prevalence and significance of some allelic variations may be population specific.

Any positive findings in your patient's test indicate genetic predisposition that could affect physiologic function and risk of disease. We do not measure every possible genetic variation. Your patient may have additional risk that is not measured by this test. Negative findings do not imply that your patient is risk-free.

The Third Wave ™ Invader DNA assay is used to detect polymorphisms in the patient's DNA sample. In this assay, a solution hybridization method is used in which two oligonucleotides hybridize in tandem with the specific DNA sequences. Subsequent Cleavase® and hybridization reactions result in generation of fluorescent signal. The biplex format of the assay enables simultaneous detection of all variants in a single reaction tube. The sensitivity and specificity of this assay is <100%.

Phase I Detoxification (Commentary for polymorphisms may not appear in this section unless the polymorphism has been indicated to have impaired activity.)

Note: In the following charts, substrates, inhibitors, and inducers are listed for each cytochrome P450 enzyme (Phase I) included in the DetoxiGenomic Profile.
Substrates are compounds that are metabolized by that enzyme. The metabolism of some of these compounds is shared by other P450 enzymes (refer to chart).
Inhibitors may or may not be substrates of that enzyme, but will reliably reduce that enzyme's activity if present.
Inducers also may or may not be substrates, but will tend to increase the enzyme's activity.

Drug Interaction Resources
http://medicine.iupui.edu/flockhart/table.htm

CYP1B1

There are 2 SNPs measured for this gene that predict risk. In this patient, the specific variants are L432V +/- and N453S negative. The commentary below reflects these results.

Health Implications: Cytochrome P450 1B1 is responsible for the 4-hydroxylation of estrogen as well as the activation of common environmental toxins such as polycyclic aromatic hydrocarbons (e.g., products from cigarette smoke, car exhaust, and charbroiled foods), polychlorinated biphenyls (e.g., PCBs), and aflatoxin B1. Polymorphisms convey a higher capacity for induction with toxin exposure, thus greater activation and potential toxicity of these compounds and greater production of 4-hydroxyestrogens.
Hyperinduction can generate oxidative stress and the 4-hydroxyestrogens may convert to quinone compounds that can cause DNA damage in breast tissue. Polymorphisms have been associated with lower 2:16α-hydroxyestrone ratios and increased risk of breast cancer, especially if xenobiotic exposure, high body mass index, long-term HRT, or concomitant CYP1A1 polymorphism. Risk is also increased for cancers of the ovary, prostate, lung and head & neck, especially in smokers.

Minimizing Risk: Do not smoke. Minimize exposure to xenobiotics (e.g., polycyclic aromatic hydrocarbons), also xenoestrogens (e.g., organochlorines), which tend to increase CYP1B1 activity. Eat a diet rich in antioxidants; consider supplementation. Redirect estrogen metabolism away from 4-hydroxylation with cruciferous vegetables and/or agents such as indole 3-carbinol (I3C), diindolylmethane (DIM), fish oils or rosemary.
Use caution with long-term HRT, especially conjugated equine estrogens which are preferentially 4-hydroxylated.

Substrates		Inhibitors	Inducers
Polycyclic aromatic hydrocarbons, (e.g., benzo(a)pyrene) Antidepressants: Amitryiptyline (Elavil) Clomipramine (Anafranil) Imipramine (Tofranil) Acetaminophen (NAPQI) Caffeine Clozapine (Clazaril) Coumarin activation Estradiol, Estrone (4-hydroxylation)	Heterocyclic amines Naproxen Propranolol (Inderal) Resveratrol Tacrine (Cognex) Testosterone Theophylline	Cimetidine Ciprofloxacin (Cipro) Erythromycin Fluvoxamine (Luvox) Pyrene Ticlopidine Grapefruit juice (naringenin) Ginseng (possible)	Omeprazole (Prilosec) Phenytoin (Dilantin) Phenobarbital Rifampin ***Polycyclic Aromatic Hydrocarbons:*** Cigarette smoke Charbroiled foods
CYP1B1: Up regulator - is involved in the 4-hydroxylation of estrogen.			

Physician Recommendations:

CYP2C9

Health Implications : Cytochrome P450 2C9 is involved in the metabolism of many drugs including blood thinners like Coumadin ®. Polymorphisms may prevent the normal metabolism of these drugs and side effects are possible. Please refer to the drug pathway chart on the following page.

Minimizing Risks: Your health care provider has a list of drugs cleared through CYP2C9. Consult your physician. You may still need these drugs, but your physician may opt to prescribe a smaller therapeutic dose. Should you need to be placed on a blood thinning agent in the future, make sure your physician knows you have a genetic polymorphism that impairs your ability to break down Coumadin ®. If you are taking aspirin to reduce the risk of colon cancer, switch to a non-aspirin alternative.

Substrates

NSAIDs
Diclofenac
Ibuprofen
Lomoxicam
Meloxicam
S-Naproxen
Piroxicam
Suprofen

Oral Hypoglycemic Agents
Tolbutamide
Glipizide

Angiotensin II Blockers
Losartan
Irbesartan

Sulfonylureas
Glyburide/glibenclamide
Glipizide
Glimepiride
Tolbutamide

Miscellaneous
Alosetron (Lotronex)
Amitriptyline (Elavil) (demethylation)
Angiotensin
Carvedilol
Celecoxib
Chloramphenicol
Clomipramine
Coumadin (Warfarin)
Desogestrel
Diazepam
Diclofenac
Dronabinol
Etravirine

Miscellaneous Continued
Febuxostat
Fluoxetine
Flurbiprofen
Fluvastatin
Formoterol
Glyburide
Hexobarbital
Hyzaar
Ibuprofen
Imipramine (Tofranil)
Indomethacin
Isoniazid
Nateglinide
Phenobarbital
Phenytoin (Dilantin)
Piroxicam
Retinoids
Rosiglitazone
Rosuvastatin (Crestor)
Sildenafil (Viagra)
Sulfa Drugs
Sulfaphenazole
Suprofen
Tamoxifen
THC (marijuana)
Torsemide (Demadex)
Valdecoxib
S-warfarin (active)
Zolpidem (Ambien, Edluar) (mostly CYP3A4)

Inhibitors

Anti-depressants
Fluvoxamine (Luvox)
Paroxetine (Paxil)
Sertraline (Zoloft)
Fluoxetine (Prozac)

Azole Antifungals
Itraconazole (Sporonox)
Ketoconazole (Nizoral)
Fluconazol (Diflucan)
Miconazole (Nystatin)
Voriconazole (Vfend)

Miscellaneous
Amiodarone
Cimetidine (Tagamet)
Chloram-phenicol
Clopidogrel (Plavix)
Delavirdine
Disulfram
Efavirenz
Etravirine
Fenofibrate
Fluorouracil
Fluvastatin
Gemfibrozil

Miscellaneous Continued
Imatinib
Isoniazid
Leflunomide
Lovastatin
Metronidazole (Flagyl)
Omeprazole
Phenylbutazone
Phenytoin (Dilantin)
Probenicid
Retonavir (Norvir)
Sulfa-methoxazole-Trimethoprim (Bactrim)
Sulfaphenazole
Sulfinpyrazone
Teniposide
Ticlopidine
Valproic acid (Depakote)
Zafirlukast

Echinacea
Garlic (possible)
Kava kava
Milk thistle (in-vitro/ probably insignificant in-vivo)
Saw palmetto (in-vitro)
St. John's wort (in-vitro studies)

Inducers

Aminoglutethimide
Aprepitant
Barbiturates
Bosentan
Carbamazepine
Ethanol
Griseovulfin
Phenobarbital
Phenytoin
Primidone
Rifabutin
Rifampin
Rifapentine
Secobarbital

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CYP2C9

Continued...

CYP2C9: Down regulator - detoxifies coumarin and suflonylureas.
Note: Individuals with deficient CYP2C9 activity may be anti-coagulated on 0.5mg of coumadin/day, as they cannot efficiently clear S-coumadin. ARBs in these people may be ineffective because a pro-drug like losartan may be poorly activated.

Physician Recommendations:

CYP3A4

Health Implications: Cytochrome P450 3A4 is used in the metabolism of 50-60% of all prescription medications, most of our steroid hormones (cortisol, estrogen, testosterone, etc.) and organophosphate insecticides (e.g., parathion). The expression of CYP3A4 activity is easily induced and inhibited by various agents, with enzyme activity varying as much as 40-fold in humans. Although modestly reduced hepatic enzyme activity has been observed in carriers, the vast majority of studies suggest minimal impact of CYP3A4 polymorphisms on enzyme expression in vivo.

Minimizing Risks: Your health care provider has been provided a list of drugs cleared through CYP3A4. Drugs that are metabolized through this pathway will be cleared more slowly when other drugs or compounds that normally inhibit the enzyme (e.g., grapefruit juice) are also being taken. Consult your physician. Please refer to the drug pathway chart on the following page.

Milk thistle has been shown in vitro to inhibit CYP3A4 activity. Caution should be exercised in prescribing it, especially if the patient is taking pharmaceuticals cleared through CYP3A4.

Slow metabolizers have a significantly increased risk (up to 6-fold) of developing prostate cancer. Polymorphisms are associated with higher clinical stage and grade of these cancers, when present. Black men have the highest prevalence of both prostate cancer and of CYP3A4 polymorphisms.

Substrates	Inhibitors	Inducers
Glucocorticoids	**Antifungals**	Aminoglutethimide
Budesonide	Clotrimazole	Aprepitant
Ciclesonide	Fluconazol (Diflucan)	Barbiturates
Cortisol	Itraconazole (Sporonox)	Bexarotene
Dexamethasone (Decadron)	Ketoconazole (Nizoral)	Bosentan
Fluticasone (Advair, Flovent)	Miconazole	Calcitriol (vitamin D3)
Hydrocodone	Posaconazole	Carbamazepine
Hydrocortisone	Voriconazole	Dexamethasone
Methylprednisolone		Efavirenz
Mometasone	**Antibiotics**	Ethosuximide
Prednisolone	(NOT azithromycin)	Etravirine
Prednisone	Ciprofloxacin	Fosphenytoin
	Clarithromycin	Glucocorticoids
Sex Steroids	Erythromycin	Glutethimide
Androstenedione	Metronidazole	Griseofulvin
DHEA	Norfloxacin	Modafinil
Estraderm, Estrace	Telithromycin	Nafcillin
Estradiol	Troleandomycin	Nevirapine
Progesterone/progestins		Oxcarbazepine
Testosterone	**HIV Anti-Virals**	Phenobarbital
	Atazanavir	Phenytoin (Dilantin)
Oral Contraceptives	Darunavir	Pioglitazone
Ethinyl estradiol	Delaviridine	Primidone
Desogestrel	Etravirine	Troglitazone
Etonogestrel	Fosamprenavir	Rifabutin
Norethindrone	Indinavir	Rifampin
Levonorgestrel	Nelfinavir	Rifapentine
	Ritonavir	Rufinamide (weak)
Antifungals	Saquinavir	Troglitazone
Itraconazole (Sporonox)		
Ketoconazole (Nizoral)	**Miscellaneous**	St John's Wort (intestinal)
Miconazole (Monistat)	Acitretin	Garlic (possible)
Voriconazole (Vfend)	Amiodarone	Licorice (possible / animal study)
	Amprenavir	
Antidepressants	Aprepitant	
Amytriptyline (Elavil)	Azelastine	
Aripiprazole (Abilify)	Chloramphenicol	
Citalopram (Celexa)	Cimetidine	
Clomipramine (Anafranil)	Conivaptan	
	Cyclosporine	

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CYP3A4 Continued...

Substrates		Inhibitors
Antidepressants cont.	**Anti-Histamines**	**Miscellaneous cont.**
Desvenlafaxine (Pristiq)	Astemizole (Hismanal)	Danazol
Imipramine (Tofranil)	Azelastine (Astepro)	Dasatinib
Nefazodone (Serzone)	Chlorpheniramine	Diltiazem
Mirtazapine (Remeron)	Fexofenadine (Allegra)	Diethyl-dithlocarbamate
Sertraline (Zoloft)	Loratadine (Claritin)	Efavirenz
Trazodone (Deseryl)		Ethinyl estradiol
Ventlafaxine (Effexor)	**HMG CoA Reductase Inhibitors**	Fluoxetine (Prozac)
	Amlodipine & atorvastatin (Caduet)	Fluvoxamine
Benzodiazepines	Atorvastatin (Lipitor)	Gestodene
Alprazolam (Xanax)	Cerivastatin (Baycol/Lipobay)	Imatinib
Clonazepam (Klonipin)	Lovastatin (Mevacor) (NOT pravastatin)	Isoniazid
Diazepam (Valium)	(NOT rosuvastatin)	Lapatinib
Midazolam (Versed)	Simvastatin (Zocor)	Methylprednisolone
Temazepam (Restoril)	Simvastatin/Niacin (Simcor)	Mibefradil
Triazolam (Halcion)		Midazolam
	Ca++ Channel Blockers	Mifepristone
Sedatives/Tranquilizers	Amlodipine	Nefazodone
Aripiprazole (Abilify)	Bepiridil (Vascor)	Nicardipine
Buspirone (Buspar)	Carbamazepine (Tegritol)	Niconazole
Haloperidol (Haldol)	Cisapride (Propulsid)	Nifedipine
Zolpidem (Ambien, Edluar)	Diltiazem	Northindrone
	Felodipine	Norfluoxetine
Antibiotics	Lercanidipine	Oxiconazole
Clarithromycin	Nicardipine	Prednisone
Clindamycin	Nifedipine	Quinine
Erythromycin	Nimodipine	Quinupristin
(NOT Azithromycin)	Nisoldipine	Roxithromycin
Telithromycin	Nitrendipine	Sertraline
	Verapamil	Synercid
Proton-Pump Inhibitors		Tamoxifin
Dexlansoprazole (Kapidex)		Troleandomycin
Esomeprazole (Nexium)		Verapamil
Lansoprazole (Prevacid)		Voriconazole
Omeprazole (Prilosec)		Zafirlukast
Pantoprazole (Protonix)		Zileuton
Rabeprazole (Aciphex)		

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CYP3A4 Continued...

Substrates		Inhibitors
HIV Anti-Virals	**Miscellaneous**	**Miscellaneous cont.**
Amprenavir (Agenerase)	Aflatoxin	Curcumin (in-vitro)
Delavirdine (Rescriptor)	Alfentanyl	Dang guai (in-vitro)
Efavirenz (Sustiva)	Almotriptan	Goldenseal/berberine (intestinal)
Indinavir (Crixivan)	Alosetron (Lotronex)	Grapefruit (intestinal)
Lopinavir (Kaletra)	Ambrisentan (Letairis)	Milk Thistle (in-vitro/probably insignificant in-vivo)
Maraviroc	Amiodarone	Garlic (possible / in vitro)
Nelfinavir (Viracept)	Aprepitant	Gallic acid
Nevirapine (Viramune)	Benzopyrene	(in wine and herbal teas- inhibition reduced by addition of ascorbic acid or GSH)
Ritonavir (Norvir)	Bromocriptine	Piper longum (pepper) (intestinal)
Saquinavir (Invirase)	Buprenorphine	Quercetin
	Cannabinoids	Saw palmetto (in-vitro)
Anti-Neoplastics	Cafergot	Star fruit
Anastrozole (Arimidex)	Caffeine	
Bexarotene	Certulizomab	
Busulfan	Cevimeline	
Cyclophosphamide	Cilostazol	
Docetaxel	Cinacalcet	
Doxorubicin	Cisapride (Propulsid)	
Etoposide	Clopidogrel (Plavix)	
Exemestane (Aromasin)	Cocaine	
Fluvestrant	Codeine-N-demethylation	
Gleevec	Cyclobenzaprine	
Ifosfamide	Cyclosporine	
Imatinib	Dapsone	
Irinotecan	Dextromethorphan	
Ixabepilone	Dextromorphan	
Letrozole (Femara)	Dihydroergotamine	
Nilotinib	Disopyramide	
Paclitaxel	Dofetilide	
Taxol	Dolasetron	
Toremifene	Domperidone	
Vinblastine	Donepezil	
Vincristine	Dronabinol	
Vinorelbine	Dronedarone	
	Drospirenone & Estradiol (Angeliq)	
	Dutasteride	
	Eplerenone	

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CYP3A4

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Substrates

Miscellaneous cont.	Miscellaneous cont.
Ergotamine	Ranolazine
Ethosuximide	Repaglinide
Fentanyl	Rifabutin
Finasteride (Propecia)	Rifampin
Flutamide	Rimonabant
Galantamine	Rivaroxaban
Glyburide (Micronase)	Risperidone
Isradipine	Salmeterol
LAAM	Sibutramine
Lapatanib	Sildenafil (Viagra)
Levobupivacaine	Sirolimus
Lidocaine	Tacrolimus
Lasofoxifene	Tamoxifen
Losartan	Tiagabine
Methadone	Tolterodine
Mifepristone	Topiramate (Topamax)-only ~5%
Modafinil	Tramadol
Montelukast (Singulair)	Trimetrexate
Nateglinide	Valdecoxib
Ondansetron	Vardenafil (Levitra)
Oxybutynin	R-warfarin
Pimozide	Zaleplon
Pioglitazone	Zileuton
Propanolol	Ziprasidone
Quetiapine	Zonisamide
Quinidine	Zotarolimus
Quinine	

CYP3A4: Down regulator - detoxifies over 50% of all prescription medications and most steroid hormones.

Physician Recommendations:

Phase II Detoxification commentary is provided only for polymorphisms with known health implications.

+ + **COMT** V158M www.genovations.com/gdv158m

Clinical Implications: Catechol-O-methyltransferase (COMT) inactivates catecholamines, catechol estrogens, and catechol drugs such as L-DOPA. A polymorphism in COMT results in reduced COMT activity, thus decreased degradation of these compounds. Risk may be increased for some neuropsychiatric disorders, impaired estrogen metabolism, cardiovascular problems, and increased sensitivity to pain.
Individuals with the (+/+) genotype have a 3-4-fold reduced clearance of catecholamines from neural synapses. As a result, risk is increased for anxiety, panic disorder, and ultra rapid cycling in bipolar disorder. Risk is also increased for fibromyalgia, breast cancer (esp. when coupled with cumulative estrogen exposure), hypertension (at least in men), and acute coronary events if also high homocysteine or heavy coffee consumption.

Minimizing Risks : Minimize sustained mental and environmental stress, as adrenaline levels may already be high. Stress hormones also require COMT for degradation, thus can decrease the methylation of estrogen compounds. Ensure adequate intake of B vitamins, magnesium, and protein.
Avoid high homocysteine (S-adenosylhomocysteine inhibits COMT). Consider betaine (TMG) along with the B vitamins, for remethylation of homocysteine. Ensure adequate antioxidants to prevent oxidation of pro-carcinogenic 4-hydroxyestrogens. Use caution with amphetamine-based medications and catechol drugs, also with conjugated equine estrogens (e.g., Premarin®), as 4-hydroxyequilenin is more likely to inhibit COMT in carriers of the polymorphism. In bipolar patients, use caution with MAO inhibitors, tricyclics, or stimulants including Ritalin. The anti-depressants mirtazapine (Remeron®) or paroxetine (Paxil®) may be less effective with this genotype. Parkinson's patients may response to lower doses of levodopa and benefit the most from vitamin B6.
Physician Recommendations:

+ - **NAT2** I114T
+ - **NAT2** R197Q

Health Implications: N-acetyltransferase 1 is found in extra-hepatic tissues, while NAT2 is found predominantly in the liver and the gut. Both are used in the Phase II acetylation of numerous environmental toxins, including heterocyclic aromatic amines. Slow acetylators do not clear toxins well and the resulting increased total toxic burden can increase the risk of lung, colon, breast, bladder, and head and neck cancers, though results have not been consistent in all studies. Urinary bladder cancer appears to have the most consistent association with slow acetylation.

Minimizing Risk: If you smoke, stop. Your risk of lung cancer is substantially higher than someone with normal NAT activity. Even occasional smoking or exposure to second hand smoke is harmful. Liberal consumption of most vegetables and fruits but especially cruciferous vegetables (broccoli, Brussels sprouts, cauliflower, watercress, and cabbage), garlic, onions, soy, grapes and berries will increase Phase II efficiency, including acetylation.
Physician Recommendations:

+- **NAT2** K268R

Health Implications: N-acetyltransferase 1 is found in extra-hepatic tissues, while N-acetyltransferase 2 is found predominantly in the liver and the gut. NAT2 is the enzyme that controls Phase II acetylation of numerous environmental toxins, including heterocyclic aromatic amines. Rapid acetylators increase O-acetylation of toxins that can actually make the toxins more reactive. These transformed toxins may increase risk of developing lung, colon, breast, bladder, head and neck cancer, though results have not been consistent in all studies. Colon cancer appears to have the most consistently reproducible association with fast acetylation.

Minimizing Risk: If you smoke, stop. Your risk of lung and breast cancer is substantially higher than someone with normal NAT activity. Do not eat fried foods and minimize red meat as these substantially increase your risk of colorectal cancer. Avoid well-done meats as these may substantially increase your risk of breast cancer. Liberal consumption of most vegetables and fruits but especially cruciferous vegetables (broccoli, Brussels sprouts, cauliflower, watercress, and cabbage), garlic, onions, soy, grapes and berries will increase Phase II efficiency, including acetylation.

Physician Recommendations:

ABSENT **GSTM1** 1p13.3

+ - **GSTP1** I105V

Health Implications: Glutathione S-transferases (GST) are responsible for detoxifying certain products of oxidative stress and a variety of electrophilic xenobiotics and carcinogens such as solvents, herbicides, pesticides, polycyclic aromatic hydrocarbons, steroids, and heavy metals. GSTM1 is located primarily in the liver, whereas GSTP1 is located primarily in the brain and lungs.

When there is no gene present on the GSTM1 chromosome it is called an "absent" allele. This results in reduced capacity for hepatic detoxification and increased risk of various cancers, chemical sensitivity, coronary artery disease in smokers, atopic asthma, and deficits in lung function. Risk appears *reduced* for colorectal- and head & neck cancer, but *only* when cruciferous vegetable intake is high.

GSTP1 polymorphisms are associated with either higher or lower enzyme activity, depending on the exposure. This GSTP1 polymorphism is associated with increased risk of various cancers, risk that is compounded by exposure to cigarette smoke and the "absent" GSTM1.

Minimizing Risk: Minimize exposure to cigarette smoke, charred food, herbicides, fungicides, insect sprays, industrial solvents, and toxic metals. Ensure availability of glutathione (GSH) precursors and cofactors, e.g., methionine, N-acetylcysteine, glutamine, glycine, magnesium, and pyridoxal-5-phosphate (B6). GSH depletion may be offset by alpha lipoic acid, milk thistle, and taurine. Allium vegetables (e.g., onions, leeks, garlic) and crucifers (e.g., broccoli, cauliflower, cabbage, kale, Brussels sprouts, radish sprouts) can increase GST activity and reduce cancer risk. Consume an antioxidant-rich diet to prevent oxidative stress.

Physician Recommendations:

+- SOD2 A16V

Health Implications: Superoxide dismutase is the primary anti-oxidant enzyme within the mitochondria of cells (where most of our energy is made). SOD2 converts reactive oxygen species into less reactive hydrogen peroxide. Polymorphisms in SOD2 (+/- and +/+) are associated with reduced SOD activity. While this may increase some risk of oxidative stress, more clinical correlations have been observed for the (-/-) genotype. This genotype has specifically been associated with increased risk of cardiomyopathy.

Minimizing Risk: Although this genotype is less sensitive to antioxidant status compared to the (-/-) genotype, liberal consumption of dietary antioxidants in colorful vegetables and fruits is still recommended. Broad-spectrum antioxidant supplements may also be helpful, as well as manganese, which serves as a cofactor for SOD2. Consult your health care provider to find the supplement regimen that best fits your overall health anti-oxidant needs.

Physician Recommendations:

DetoxiGenomic™ Profile

Detoxification & Your Health

Detoxification is the metabolic process your body uses to transform and eliminate toxins. The process can occur in two steps, called Phase I and Phase II.

- **Phase I** is our first line of defense against toxins. Enzymes in the liver act on the chemical structure of a toxin to make it easier to excrete. For some compounds, including many drugs, Phase I is all that's needed to eliminate the toxin. Other toxins are actually made more reactive after Phase I and require an additional step.

- **Phase II** is our second line of defense against toxins. Phase II further alters the chemical structure of a toxin by adding, or "conjugating," water-soluble molecules to the toxin.

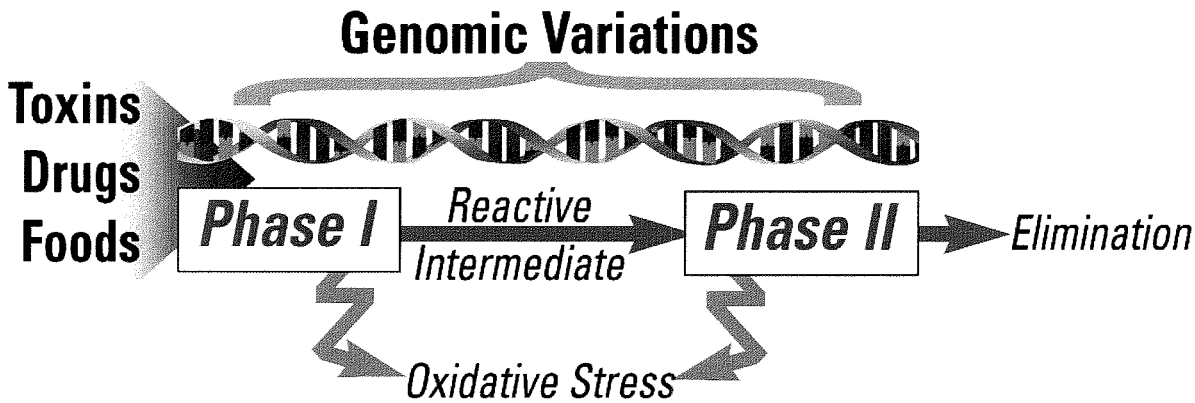
Toxic substances come from the environment, from the foods and medicines we consume, and from the body itself (natural waste products of metabolism). Examples include:

- pollution
- pesticides
- herbicides
- solvents
- pharmaceutical drugs
- charbroiled foods

DetoxiGenomic™ Profile
Personalized for

ANNA

Brian Popiel, ND



Your DetoxiGenomic™ Profile identifies genetic variations that may affect your ability to detoxify specific toxins, medications, and even foods. Working with your healthcare provider, you can develop a personalized treatment plan that matches your environment to your genes in order to optimize your health.

GENOVATIONS™

Genova Diagnostics®
Improving Healthcare for Chronic Disease

DetoxiGenomic™ Profile

Patient's Copy

GENOVATIONS™

63 Zillicoa Street
Asheville, NC 28801

Patient: **ANNA**

DOB: January 26, 1952
Sex: F
MRN: 1232058296

Order Number: F6270034
Completed: January 04, 2013
Received: December 27, 2012
Collected: December 26, 2012

Security Code: 7059323

Sonoran Naturopathic Center
Brian Popiel ND
9316 E Raintree Dr
Suite 140
Scottsdale, AZ 85260

PHASE I Detoxification: The First Line of Defense

In Phase I detoxification, enzymes, known collectively as the cytochrome P-450 system, use oxygen to modify toxic compounds, drugs, or steroid hormones. Many toxins must undergo Phase II detoxification after a reactive site has been formed. Because there are many different toxic compounds the body might encounter, there are many variants of Phase I enzymes.

Cytochrome P-450		
Result	Gene	internet information
✔	**CYP1A1** *	www.genovations.com/gdgen01
●	**CYP1B1** *	www.genovations.com/gdgen02
✔	**CYP2A6**	www.genovations.com/gdgen10
●	**CYP2C9** *	www.genovations.com/gdgen05
✔	**CYP2C19** *	www.genovations.com/gdgen06
✔	**CYP2D6**	www.genovations.com/gdgen03
✔	**CYP2E1**	www.genovations.com/gdgen04
●	**CYP3A4** *	www.genovations.com/gdgen07

Your Results: Polymorphisms (SNPs) in the genes coding for a particular enzyme can increase or, more commonly, decrease the activity of that enzyme. Both increased and decreased activity may be harmful. Increased Phase I clearance without increased clearance in Phase II can lead to the formation of toxic intermediates that may be more toxic than the original toxin. Decreased Phase I clearance will cause toxic accumulation in the body. Adverse reactions to drugs are often due to a decreased capacity for clearing them from the system.

General Therapies to Improve Detoxification:

Foods that generally improve Phase I detoxification and as well improve the efficiency of Phase II conjugation are generally recommended for individuals with CYP SNPs. These include most vegetables and fruits, but especially cruciferous vegetables (broccoli, Brussels sprouts, cauliflower, watercress, and cabbage), garlic, onions, soy, grapes, berries, green and black tea, and many herbs and spices like rosemary, basil, turmeric, cumin, poppy seeds, and black pepper. Indeed, improving Phase I and Phase II detoxification helps explain why vegetables and fruits protect against many cancers.

Key		
	✔	Optimal genomic potential - no polymorphism detected
	●	Polymorphism detected in this enzyme, increasing your susceptibility to toxins, if exposed
	*	Multiple SNP locations were evaluated for these genes
	NR	See commentary if applicable

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PHASE II Detoxification: Conjugation of Toxins and Elimination

In Phase II detoxification, large water-soluble molecules are added to toxins, usually at the reactive site formed by Phase I reactions. After Phase II modifications, the body is able to eliminate the transformed toxins in the urine or the feces (through the bile).

Methylation

Result	Gene	SNP Location	Internet Information	Affects
++	**COMT**	V158M	www.genovations.com/gdv158m	Liver/Gut

Your Results: Catechol-O-methyl transferase is the enzyme primarily responsible for breaking down the neurotransmitters dopamine, epinephrine, and norepinephrine.

Acetylation (N-acetyltransferase)

SLOW METABOLIZER POLYMORPHISM

Result	Gene	SNP Location	Internet Information	Affects
−−	**NAT1**	R64W	www.genovations.com/gdr64w	All Cells
−−	**NAT1**	R187Q	www.genovations.com/gdr187q	Liver/Gut
+−	**NAT2**	I114T	www.genovations.com/gdi114t	Liver/Gut
+−	**NAT2**	R197Q	www.genovations.com/gdr197q	Liver/Gut
−−	**NAT2**	G286E	www.genovations.com/gdg286e	Liver/Gut
−−	**NAT2**	R64Q	www.genovations.com/gdr64q	Liver/Gut

FAST METABOLIZER POLYMORPHISM

+−	**NAT2**	K268R	www.genovations.com/gdk268r	Liver/Gut

Your Results: N-acetyl Transferase detoxifies many environmental toxins, including tobacco smoke and exhaust fumes. Polymorphisms can result in slower than normal or faster than normal addition of an acetyl group to these toxins. Slow acetylators have a build up of toxins in the system and rapid acetylators add acetyl groups so rapidly that they make mistakes in the process. Both slow and rapid acetylators are at increased risk for toxic overload if they are exposed to environmental toxins. If the toxin exposure is reduced, the risk is reduced.

Glutathione Conjugation (Glutathione s-transferase)

Result	Gene	Location	Internet Information	Affects
ABSENT	**GSTM1**	1p13.3	www.genovations.com/gdrgstm1	Liver/Kidney
+−	**GSTP1**	I105V	www.genovations.com/gdrgstp1	Brain/Skin
−−	**GSTP1**	A114V	www.genovations.com/gda114v	Brain/Skin

Your Results: Glutathione-S-transferase detoxifies many water-soluble environmental toxins, including many solvents, herbicides, fungicides, lipid peroxides, and heavy metals (e.g., mercury, cadmium, and lead). The various forms of GST work together to eliminate toxins. Decreased glutathione conjugation capacity may increase toxic burden and increase oxidative stress.

Oxidative Protection

Result	Gene	SNP Location	Internet Information	Affects
−−	**SOD1**	G93A	www.genovations.com/gdg93a	Cytosol
−−	**SOD1**	A4V	www.genovations.com/gda4v	Cytosol
+−	**SOD2**	A16V	www.genovations.com/gda16v	Mitochondria

Your Results: Superoxide Dismutase is an enzyme that protects cells from increased oxidative stress and free radical damage to cell structures like membranes, mitochondria, DNA, and proteins.

Key

−− Neither chromosome carries the genetic variation.
+− One chromosome (of two) carries the genetic variation.
++ Both chromosomes carry the genetic variation.

(You inherit one chromosome from each parent)

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This test has been developed and its performance characteristics determined by Genova Diagnostics, Inc. It has not been cleared or approved by the U.S. Food and Drug Administration.

Commentary is provided to the practitioner for educational purposes, and should not be interpreted as diagnostic or treatment recommendations. Diagnosis and treatment decisions are the responsibility of the practitioner.

The accuracy of genetic testing is not 100%. Results of genetic tests should be taken in the context of clinical representation and familial risk. The prevalence and significance of some allelic variations may be population specific.

Any positive findings in your patient's test indicate genetic predisposition that could affect physiologic function and risk of disease. We do not measure every possible genetic variation. Your patient may have additional risk that is not measured by this test. Negative findings do not imply that your patient is risk-free.

The Third Wave™ Invader DNA assay is used to detect polymorphisms in the patient's DNA sample. In this assay, a solution hybridization method is used in which two oligonucleotides hybridize in tandem with the specific DNA sequences. Subsequent Cleavase® and hybridization reactions result in generation of fluorescent signal. The biplex format of the assay enables simultaneous detection of all variants in a single reaction tube. The sensitivity and specificity of this assay is <100%.

Phase I Detoxification (Commentary for polymorphisms may not appear in this section unless the polymorphism has been indicated to have impaired activity.)

CYP1B1

There are 2 SNPs measured for this gene that predict risk. In this patient, the specific variants are L432V +/- and N453S negative. The commentary below reflects these results.

Health Implications: Cytochrome P450 1B1 is responsible for the 4-hydroxylation of estrogen as well as the activation of common environmental toxins such as polycyclic aromatic hydrocarbons (e.g., products from cigarette smoke, car exhaust, and charbroiled foods), polychlorinated biphenyls (e.g., PCBs), and aflatoxin B1. Polymorphisms convey a higher capacity for induction with toxin exposure, thus greater activation and potential toxicity of these compounds and greater production of 4-hydroxyestrogens.

Minimizing Risk: Do not smoke. Minimize exposure to xenobiotics (e.g., polycyclic aromatic hydrocarbons), also xenoestrogens (e.g., organochlorines), which tend to increase CYP1B1 activity. Eat a diet rich in antioxidants; consider supplementation. Redirect estrogen metabolism away from 4-hydroxylation with cruciferous vegetables and/or agents such as indole 3-carbinol (I3C), diindolylmethane (DIM), fish oils, or rosemary.
Physician Recommendations:

CYP2C9

Health Implications : Cytochrome P450 2C9 is involved in the metabolism of many drugs including blood thinners like Coumadin®. Polymorphisms may prevent the normal metabolism of these drugs and side effects are possible.

Minimizing Risks: Your health care provider has a list of drugs cleared through CYP2C9. Consult your physician. You may still need these drugs, but your physician may opt to prescribe a smaller therapeutic dose. Should you need to be placed on a blood thinning agent in the future, make sure your physician knows you have a genetic polymorphism that impairs your ability to break down Coumadin®. If you are taking aspirin to reduce the risk of colon cancer, switch to a non-aspirin alternative.
Physician Recommendations:

CYP3A4

Health Implications: Cytochrome P450 3A4 is used in the metabolism of 50-60% of all prescription medications, most of our steroid hormones (cortisol, estrogen, testosterone, etc.) and organophosphate insecticides (e.g., parathion). The expression of CYP3A4 activity is easily induced and inhibited by various agents, with enzyme activity varying as much as 40-fold in humans. Although modestly reduced hepatic enzyme activity has been observed in carriers, the vast majority of studies suggest minimal impact of CYP3A4 polymorphisms on enzyme expression in vivo.

Minimizing Risks: Your health care provider has been provided a list of drugs cleared through CYP3A4. Drugs that are metabolized through this pathway will be cleared more slowly when other drugs or compounds that normally inhibit the enzyme (e.g., grapefruit juice) are also being taken. Consult your physician.

Physician Recommendations:

Phase II Detoxification commentary is provided only for polymorphisms with known health implications.

+ + **COMT** V158M

Health Implications: Catechol-O-methyltransferase (COMT) inactivates catecholamines, catechol estrogens, and catechol drugs such as L-DOPA. A polymorphism in COMT results in reduced COMT activity, thus decreased degradation of these compounds. Risk may be increased for some neuropsychiatric disorders, impaired estrogen metabolism, cardiovascular problems, and increased sensitivity to pain.

Minimizing Risks: Minimize sustained mental and environmental stress, as adrenaline levels may already be high. Stress hormones also require COMT for their degradation, thus can decrease the methylation of estrogen compounds. Ensure adequate intake of B vitamins, magnesium, and protein.
Physician Recommendations:

+ - **NAT2** I114T
+ - **NAT2** R197Q

Health Implications: N-acetyltransferase 1 is found in extra-hepatic tissues, while NAT2 is found predominantly in the liver and the gut. Both are used in the Phase II acetylation of numerous environmental toxins, including heterocyclic aromatic amines. Slow acetylators do not clear toxins well and the resulting increased total toxic burden can increase the risk of lung, colon, breast, bladder, and head and neck cancers, though results have not been consistent in all studies. Urinary bladder cancer appears to have the most consistent association with slow acetylation.

Minimizing Risk: If you smoke, stop. Your risk of lung cancer is substantially higher than someone with normal NAT activity. Even occasional smoking or exposure to second hand smoke is harmful. Liberal consumption of most vegetables and fruits but especially cruciferous vegetables (broccoli, Brussels sprouts, cauliflower, watercress, and cabbage), garlic, onions, soy, grapes and berries will increase Phase II efficiency, including acetylation.
Physician Recommendations:

+ - **NAT2** K268R

Health Implications: N-acetyltransferase 1 is found in extra-hepatic tissues, while N-acetyltransferase 2 is found predominantly in the liver and the gut. NAT2 is the enzyme that controls Phase II acetylation of numerous environmental toxins, including heterocyclic aromatic amines. Rapid acetylators increase O-acetylation of toxins that can actually make the toxins more reactive. These transformed toxins may increase risk of developing lung, colon, breast, bladder, head and neck cancer, though results have not been consistent in all studies. Colon cancer appears to have the most consistently reproducible association with fast acetylation.

Minimizing Risk: If you smoke, stop. Your risk of lung and breast cancer is substantially higher than someone with normal NAT activity. Do not eat fried foods and minimize red meat as these substantially increase your risk of colorectal cancer. Avoid well-done meats as these may substantially increase your risk of breast cancer. Liberal consumption of most vegetables and fruits but especially cruciferous vegetables (broccoli, Brussels sprouts, cauliflower, watercress and cabbage), garlic, onions, soy, grapes and berries will increase Phase II efficiency, including acetylation.

Physician Recommendations:

ABSENT **GSTM1** 1p13.3

+ - **GSTP1** I105V

Health Implications: Glutathione S-transferases (GST) are responsible for detoxifying certain products of oxidative stress and a variety of electrophilic xenobiotics and carcinogens such as solvents, herbicides, pesticides, polycyclic aromatic hydrocarbons, steroids, and heavy metals. GSTM1 is located primarily in the liver, whereas GSTP1 is located primarily in the brain and lungs.

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GSTP1 polymorphisms are associated with either higher or lower enzyme activity, depending on the exposure. This GSTP1 polymorphism is associated with increased risk of various cancers, risk that is compounded by exposure to cigarette smoke and the "absent" GSTM1.

Minimizing Risk: Minimize exposure to cigarette smoke, charred food, herbicides, fungicides, insect sprays, industrial solvents, and toxic metals. Ensure availability of glutathione (GSH) precursors and cofactors, e.g., methionine, N-acetylcysteine, glutamine, glycine, magnesium, and pyridoxal-5-phosphate (B6). GSH depletion may be offset by alpha lipoic acid, milk thistle, and taurine. Allium vegetables (e.g., onions, leeks, garlic) and crucifers (e.g., broccoli, cauliflower, cabbage, kale, Brussels sprouts, radish sprouts) can increase GST activity and reduce cancer risk. Consume an antioxidant-rich diet to prevent oxidative stress.

Physician Recommendations:

+- **SOD2** A16V

Health Implications: Superoxide dismutase is the primary anti-oxidant enzyme within the mitochondria of cells (where most of our energy is made). SOD2 converts reactive oxygen species into less reactive hydrogen peroxide. Polymorphisms in SOD2 (+/- and +/+) are associated with reduced SOD activity. While this may increase some risk of oxidative stress, more clinical correlations have been observed for the (-/-) genotype. This genotype has specifically been associated with increased risk of cardiomyopathy.

Minimizing Risk: Although this genotype is less sensitive to antioxidant status compared to the (-/-) genotype, liberal consumption of dietary antioxidants in colorful vegetables and fruits is still recommended. Broad-spectrum antioxidant supplements may also be helpful, as well as manganese, which serves as a cofactor for SOD2. Consult your health care provider to find the supplement regimen that best fits your overall health anti-oxidant needs.

Physician Recommendations: