



63 Zillicoa Street
Asheville, NC 28801
© Genova Diagnostics

Patient: **JANE
DOE**
DOB:
Sex: F
MRN:

Order Number:
Completed:
Received:
Collected:

Security Code:

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 sulfonyleureas.

(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

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.

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.

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.



Genova
Diagnostics®

Improving Healthcare for Chronic Disease



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	

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

Acetylation (N-acetyl transferase)					
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	

(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/gdgstm1	Liver/Kidney	
++	GSTP1	I105V	www.genovations.com/gdgstp1	Brain/Skin	
+ -	GSTP1	A114V	www.genovations.com/gda114v	Brain/Skin	

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

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.

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.

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

www.genovations.com/gdgen02

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 2:16 α -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: Amitriptyline (Elavil) Clomipramine (Anafranil) Imipramine (Tofranil) Acetaminophen (NAPQI) Caffeine Clozapine (Claziril) 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:

CYP2C9www.genovations.com/gdgen05

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	Inhibitors	Inducers
<p><u>NSAIDs</u> Diclofenac Ibuprofen Lomoxicam Meloxicam S-Naproxen Piroxicam Suprofen</p> <p><u>Oral Hypoglycemic Agents</u> Tolbutamide Glipizide</p> <p><u>Angiotensin II Blockers</u> Losartan Irbesartan</p> <p><u>Sulfonylureas</u> Glyburide/glibenclamide Glipizide Glimepiride Tolbutamide</p> <p><u>Miscellaneous</u> Alosetron (Lotronex) Amitriptyline (Elavil) (demethylation) Angiotensin Carvedilol Celecoxib Chloramphenicol Clomipramine Coumadin (Warfarin) Desogestrel Diazepam Diclofenac Dronabinol Etravirine</p>	<p><u>Miscellaneous Continued</u> 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) Torsemidex (Demadex) Valdecoxib S-warfarin (active) Zolpidem (Ambien, Edluar) (mostly CYP3A4)</p> <p><u>Anti-depressants</u> Fluvoxamine (Luvox) Paroxetine (Paxil) Sertraline (Zoloft) Fluoxetine (Prozac)</p> <p><u>Azole Antifungals</u> Itraconazole (Sporonox) Ketoconazole (Nizoral) Fluconazol (Diflucan) Miconazole (Nystatin) Voriconazole (Vfend)</p> <p><u>Miscellaneous</u> Amiodarone Cimetidine (Tagamet) Chloramphenicol Clopidogrel (Plavix) Delavirdine Disulfiram Efavirenz Etravirine Fenofibrate Fluorouracil Fluvastatin Gemfibrozil</p>	<p><u>Miscellaneous Continued</u> 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</p> <p>Echinacea Garlic (possible) Kava kava Milk thistle (in-vitro/ probably insignificant in-vivo) Saw palmetto (in-vitro) St. John's wort (in-vitro studies)</p> <p>Aminoglutethimide Aprepitant Barbiturates Bosentan Carbamazepine Ethanol Griseovulfin Phenobarbital Phenytoin Primidone Rifabutin Rifampin Rifapentine Secobarbital</p>

Continued...

 **CYP2C9**

Continued...

CYP2C9: Down regulator - detoxifies coumarin and sulfonylureas.

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:

● CYP3A4www.genovations.com/gdgen07

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

Continued...

● CYP3A4

Continued...

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

Continued...

● CYP3A4

Continued...

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

Continued...

● CYP3A4

Continued...

Substrates**Miscellaneous cont.**

Ergotamine
 Ethosuximide
 Fentanyl
 Finasteride (Propecia)
 Flutamide
 Galantamine
 Glyburide (Micronase)
 Isradipine
 LAAM
 Lapatanib
 Levobupivacaine
 Lidocaine
 Lasofoxifene
 Losartan
 Methadone
 Mifepristone
 Modafinil
 Montelukast (Singulair)
 Nateglinide
 Ondansetron
 Oxybutynin
 Pimozide
 Pioglitazone
 Propranolol
 Quetiapine
 Quinidine
 Quinine

Miscellaneous cont.

Ranolazine
 Repaglinide
 Rifabutin
 Rifampin
 Rimonabant
 Rivaroxaban
 Risperidone
 Salmeterol
 Sibutramine
 Sildenafil (Viagra)
 Sirolimus
 Tacrolimus
 Tamoxifen
 Tiagabine
 Tolterodine
 Topiramate (Topamax)-only ~5%
 Tramadol
 Trimetrexate
 Valdecoxib
 Vardenafil (Levitra)
 R-warfarin
 Zaleplon
 Zileuton
 Ziprasidone
 Zonisamide
 Zotarolimus

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, and increased sensitivity to pain.

Individuals carrying the M allele (+) have moderately reduced clearance of catecholamines from neural synapses. The polymorphism is associated with improved cognition due to higher amounts of synaptic dopamine. Risk is increased, however, for anxiety, mood disorders, and ultra rapid cycling in bipolar disorder. Risk is also increased for breast cancer (if prolonged estrogen exposure), hypertension (at least in men), and fibromyalgia.

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.

Avoid high homocysteine (S-adenosylhomocysteine inhibits COMT). Ensure adequate antioxidants to prevent oxidation of pro-carcinogenic 4-hydroxyestrogens. Use caution with amphetamine-based medications and catechol drugs. Use caution with conjugated equine estrogens (e.g., Premarin®), as 4-hydroxyequilenin is more likely to inhibit COMT in carriers of the polymorphism. Also be careful with amphetamine-based medications. Breast cancer risk is increased with long-term estrogen replacement and in women who also have a GST polymorphism. Vitamin B6 appears to be helpful to Parkinson's patients.

Physician Recommendations:

+ - NAT2 I114T

www.genovations.com/gdi114t

+ - NAT2 R197Q

www.genovations.com/gdr197q

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	www.genovations.com/gdk268r
-----------------	-------	--

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	www.genovations.com/gdgstm1
---------------	--------------	--------	--

+ -	GSTP1	A114V	www.genovations.com/gda114v
------------	--------------	-------	--

+ +	GSTP1	I105V	www.genovations.com/gdgstp1
------------	--------------	-------	--

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. These GSTP1 genotypes are associated with increased risk of various cancers, risk that is compounded by exposure to cigarette smoke and the "absent" GSTM1. Risk may also be increased for late-onset Alzheimer's, and Parkinson's disease in smokers.

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 reduced 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

www.genovations.com/gda16v

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: