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.

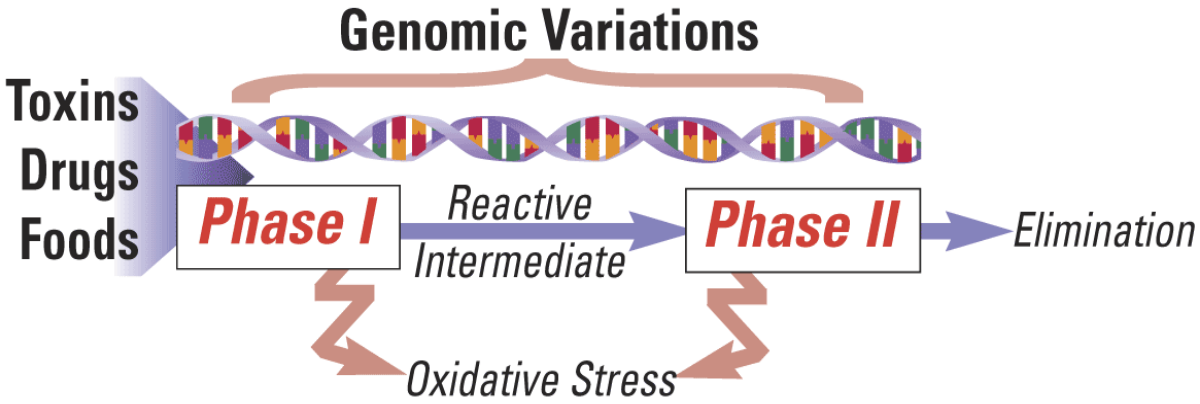
Toxic substances come from the environment, from the foods and medicines we consume, and from the body itself (natural waste products of metabolism). Examples include:

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

DetoxiGenomic™ Profile
Personalized for

SHAWN BEAN

Michael Overbeck, MD



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.

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Genova Diagnostics®
Innovative Testing for Optimal Health

DetoxiGenomic™ Profile

Patient's Copy

GENOVATIONS™

63 Zillicoa Street
Asheville, NC 28801

Patient: **SHAWN BEAN**
DOB: February 10, 1973
Sex: M
MRN: 0000713446

Order Number: C9030445
Completed: September 15, 2010
Received: September 03, 2010
Collected: August 23, 2010

Security Code: 3358307

Michael Overbeck MD
1100 Fayette St
Conshohocken, PA 19428

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-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

Result	Gene	SNP Location	Internet Information	Affects
++	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
PRESENT	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

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 99.7%.

Dr. Amy Peace-Brewer
Laboratory Director

Dr. Patrick Hanaway
Chief Medical Officer

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

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.

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:

CYP2C19 www.genovations.com\gdgen06

Health Implications : Cytochrome P450 2C19 is involved in the metabolism of many drugs like proton pump inhibitors (e.g., Prilosec™) and anticonvulsants (e.g., valium). Slow metabolizers may experience side-effects at commonly used dosages. Therapeutic effectiveness is often achieved at significantly lower doses.

Minimizing Risks: Your health care provider has a list of drugs cleared through CYP2C19. Consult your physician. You may still need these drugs, but your physician may opt to prescribe a smaller therapeutic dose.
Physician Recommendations:

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

+ + NAT2 I114T www.genovations.com/gdi114t

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:

PRESENT	**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.

The test indicates that the GSTM1 gene is present, although it is not clear whether the gene is present on one or both chromosomes. This suggests normal GSTM1 enzyme activity and hepatic detoxification of xenobiotics and toxic metals.

GSTP1 polymorphisms are associated with either higher or lower enzyme activity, depending on the exposure. This genotype is associated with increased risk of various cancers, especially with cigarette smoke exposure. 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:

DetoxiGenomic™ Profile

Physician's Copy

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63 Zillicoa Street
Asheville, NC 28801

Patient: **SHAWN BEAN**
DOB: February 10, 1973
Sex: M
MRN: 0000713446

Order Number: C9030445
Completed: September 15, 2010
Received: September 03, 2010
Collected: August 23, 2010

Security Code: 3358307

Michael Overbeck MD
1100 Fayette St
Conshohocken, PA 19428

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 coumarin and sulfonureas.

(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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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

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

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

Result	Gene	SNP Location	Internet Information	Affects
++	NAT2	K268R	www.genovations.com/gdk268r	Liver/Gut

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

(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
PRESENT	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

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

(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.

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 practicioner for educational purposes, and should not be interpreted as diagnostic or treatment recommendations. Diagnosis and treatment decisions are the responsibility of the practicioner.

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 99.7%.

Dr. Amy Peace-Brewer
Laboratory Director

Dr. Patrick Hanaway
Chief Medical Officer

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 2:16α-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
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:

CYP2C19

www.genovations.com\gdgen06

Health Implications : Cytochrome P450 2C19 is involved in the metabolism of many drugs like proton pump inhibitors (e.g. Prilosec®) and anticonvulsants (e.g. Valium®). Slow metabolizers may experience side-effects at commonly used dosages. Therapeutic effectiveness is often achieved at significantly lower doses.

Poor metabolizers have an increased risk of developing scleroderma and a mildly increased risk of acute leukemia.

Minimizing Risks: Your health care provider has a list of drugs cleared through CYP2C19. Consult your physician. You may still need these drugs, but your physician may opt to prescribe a smaller therapeutic dose.

Substrates		Inhibitors		Inducers
Anti-Epileptics	**Miscellaneous**	**SSRI Antidepressants**	**Miscellaneous**	Carbamazepine
Diazepam (Valium)	Ambrisentan (Letairis)	Fluoxetine (Prozac)	Chloramphenicol	Norethindrone (NOT Pentobarbital)
Phenytoin (Dilantin)	Carisoprodol	Sertraline (Zoloft)	Delavirdine	
S-mephenytoin	Chloramphenicol	Paroxetine (Paxil)	Efavirenz	**Prednisone**
Phenobarbitone	Cilostazol	Fluvoxamine (Luvox)	Felbamate	Phenobarbital
	Citalopram	Citalopram (Celexa)	Fluvastatin	Phenytoin
Proton Pump Inhibitors	Cyclophosphamide		Indomethacin	Rifampin
Esomeprazole (Nexium)	Felbamate	**Proton Pump Inhibitors**	Isoniazid	
Omeprazole (Prilosec)	Formoterol	Omeprazole (Prilosec)	Letrozole	Ginkgo biloba
Lansoprazole (Prevacid)	Hexobarbital	Lansoprazole (Prevacid)	Modafinil	
Pantoprazole (Protonix)	Indomethacin	Pantoprazole	Oxcarbazepine	
Rabeprazole (Aciphex)	R-mephobarbital	Rabeprazole	Probenicid	
E-3810	Moclobemide		Retonavir (Norvir)	
	Nelfinavir	Cimetidine (Tagamet)	Telmisartan	
Tricyclic antidepressants	Nilutamide		Ticlopidine	
Amitriptyline (Elavil)	Pentamidine	**Anti-Fungals**	Topiramate	
Clomipramine (Anafranil)	Propanolol (Inderal)	Fluconazole (Diflucan)	Garlic (possible)	
Desipramine (Norpramin)	Premarin	Ketoconazole (Nizoral)	St. John's wort (possible)	
Imipramine (Tofranil)	Primidone	Voriconazole	Epigallocatechin (possible)	
	Progesterone		Ginkgo biloba	
	Proguanil		Kava kava	
	Propanolol			
	Temazepam (Restoril)			
	Teniposide			
	Thioridazine			
	Tolbutamide			
	R-warfarin			
	Voriconazole			

CYP2C19: Down regulator - detoxifies proton pump inhibitors (e.g. Prilosec®) and many anti-convulsants (e.g. Valium®). Low activity allows eradication of H. pylori with 2 drugs in many cases. B12 deficiency is theoretically possible with long-term PPI treatment. Risk of phenytoin toxicity.

Physician Recommendations:

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

+ + NAT2 I114T www.genovations.com/gdi114t

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:

PRESENT	**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.

The test indicates that the GSTM1 gene is present, although it is not clear whether the gene is present on one or both chromosomes. This suggests normal GSTM1 enzyme activity and hepatic detoxification of xenobiotics and toxic metals.

GSTP1 polymorphisms are associated with either higher or lower enzyme activity, depending on the exposure. This genotype is associated with increased risk of various cancers, especially with cigarette smoke exposure. 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: