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.

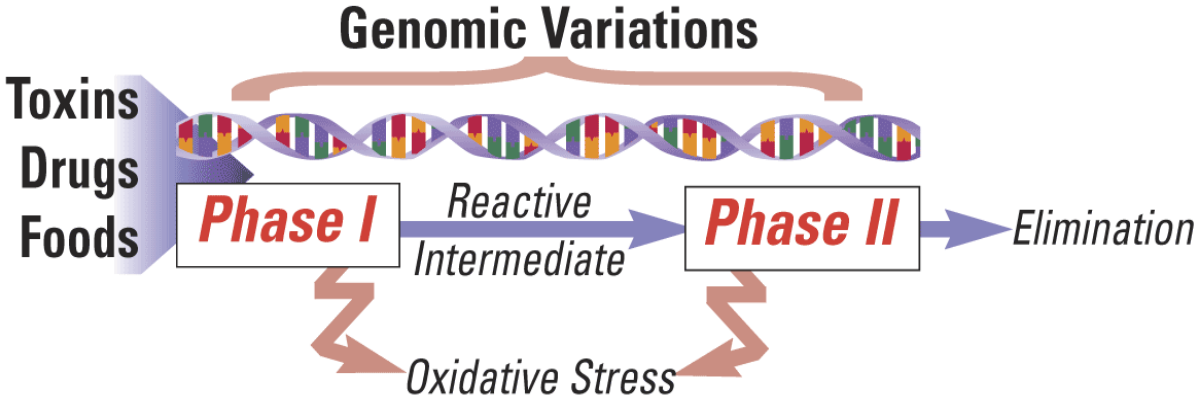
Toxic substances come from the environment, from the foods and medicines we consume, and from the body itself (natural waste products of metabolism). Examples include:

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

DetoxiGenomic™ Profile
Personalized for

NONEGIVEN 15A BLUETICK

Beatrice Golomb, MD, PhD



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

DetoxiGenomic™ Profile (Buccal Cells)

Patient's Copy

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63 Zillicoa Street
Asheville, NC 28801

Patient: **NONEGIVEN 15A BLUETICK**
DOB: Not Provided
Sex: Not Given
MRN: 1232474352

Order Number: I4160761
Completed: April 24, 2015
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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.

Cytochrome P-450	
Result	Gene
✔	**CYP1A1** *
●	**CYP1B1** *
✔	**CYP2A6**
✔	**CYP2C9** *
✔	**CYP2C19** *
✔	**CYP2D6**
✔	**CYP3A4** *

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	Affects
−−	**COMT**	V158M	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	Affects
−−	**NAT1**	R64W	All Cells
−−	**NAT1**	R187Q	Liver/Gut
+−	**NAT2**	I114T	Liver/Gut
+−	**NAT2**	R197Q	Liver/Gut
−−	**NAT2**	G286E	Liver/Gut
−−	**NAT2**	R64Q	Liver/Gut

FAST METABOLIZER POLYMORPHISM

Result	Gene	SNP Location	Affects
++	**NAT2**	K268R	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	Affects
ABSENT	**GSTM1**	1p13.3	Liver/Kidney
+−	**GSTP1**	I105V	Brain/Skin
−−	**GSTP1**	A114V	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	Affects
−−	**SOD1**	G93A	Cytosol
−−	**SOD1**	A4V	Cytosol
+−	**SOD2**	A16V	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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Lab Comments

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.

DNA sequencing is used to detect polymorphisms in the patient's DNA sample. 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:

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

+ -	**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: