# DetoxiGenomic™ Profile

*Patient's Copy*

GENOVATIONS™

63 Zillicoa Street
Asheville, NC 28801


Patient: SAMPLE
PATIENT
DOB:
Sex:
MRN:

## *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

| | | | |
|---|---|---|---|
| −− | **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 |
|---|---|---|---|
| PRESENT | **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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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:**

### 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:**

**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, 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** 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:**

| | | | |
|---|---|---|---|
| **PRESENT** | **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.

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 GSTP1 polymorphism is associated with increased risk of various cancers, risk that is compounded by exposure to cigarette smoke.

**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:**

## CHECKLIST (PRIOR TO SHIPPING)

**1. Cotton Swabs**

❑ Swabs are returned to the original Cotton Swab Package

❑ Cotton Swabs Package is sealed in the Letter Envelope

**2. Specimen Collection Label**

❑ Label is filled out and adhered to the Letter Envelope

**3. Test Requisition Form with Payment**

❑ Test Requisition Form is complete - Test is marked, Patient's first and last name, date of birth, gender, date of collection

❑ Test requistion is placed in the collection kit envelope.

❑ Payment is included


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**ASHEVILLE • ATLANTA • LONDON**

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This specimen collection kit can be used for the following tests:

**CardioGenomicPlus™ Profile ***

**DetoxiGenomic® Profile ***

**EstroGenomic™ Profile ***

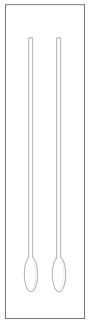
**Sub Panel Estrogen Metabolism ***

**Sub Panel Hypercoagulation ***

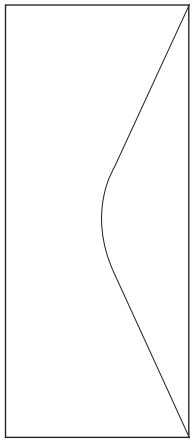
**ImmunoGenomic® Profile ***

**NeuroGenomic™ Profile ***

* Not Available in New York



Cotton Swabs and Package



Letter Envelope

## SPECIMEN

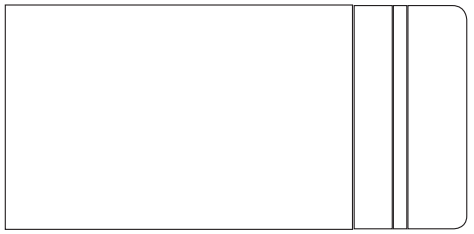
**Buccal swab**

## COLLECTION MATERIALS

- 2 Cotton Swabs
- Returnable Cotton Swabs Package
- Letter Envelope

## SHIPPING MATERIALS*

- Collection Kit Package
- Test Requisition Form
- FedEx® Billable Stamp
- Specimen Collection Label



Collection Kit Package

*International shipping may vary, please see shipping instructions for more details.*

## IMPORTANT:

All patient specimens require two unique identifiers (***patient's name and date of birth***), as well as ***date of collection***. **Patient's first and last name, date of birth, gender,** and **date of collection** must be recorded on the **Test Requisition Form** as well as all tube(s) and/or cup(s), using a permanent marker, or the test may not be processed.

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*Please read all instructions carefully before beginning.*

## PATIENT PREPARATION

- Specimen **must be collected immediately** upon rising. **Do not practice** normal oral hygiene routine, **do not eat or drink.**
- **Prior to collection:** The night before collection, use your normal nightly routine of brushing and flossing of teeth, but **do not use mouthwash.**
- **Morning of Collection:** On the morning of collection, do not eat, brush or floss your teeth, use mouthwash, chew gum or use any tobacco, or coffee products. You may drink ONLY water before specimen collection. Just prior to collection, wash hands completely with hand soap.

## SALIVA COLLECTION

1. **Write** patient's **first and last name, date of birth**, **gender** and **date of collection** on the Test Requisition Form.
   **IMPORTANT**: To ensure accurate test results you **MUST** provide the requested information.
2. **Peel** open the package labeled, "Sterile Cotton Tipped Applicator." *Only peel back the package far enough to remove the cotton swab applicator*. Keep the packet intact. (See Figure 1).
3. **Remove** one applicator taking care to avoid contact with the cotton tip.
4. **Open** your mouth widely and insert applicator. For at least 30 seconds, **aggressively scrape** the inside of your cheek using a back and forth, and up and down motion. Be sure to **rotate** the applicator several times to ensure the swab collects a sufficient amount of cheek cells. In addition, **swab** between the cheek and gums. (See Figure 2)
   **Note**: If there is not enough DNA collected on the applicator, a recollection will be required.
5. **Remove** the applicator from your mouth and allow cotton tips to air dry for 15-20 minutes (See Figure 3A) before placing it back into the original packaging, cotton swab first. (See Figure 3B)
6. **Repeat** the collection process (steps 1-3) with the second applicator on your opposite cheek.

## SPECIMEN PREPARATION

1. **Place** the package containing the two collected specimen swabs into the letter envelope. Seal the letter envelope.
2. **Print name and collection date** on specimen collection label. **Place** the specimen collection label on the letter envelope.
3. **Seal** and **place** the letter envelope into the collection kit envelope.
4. **Fill** out the Test Requisition by completing all patient and billing information, including the date of collection. **Sign** the form and **place** it back inside the collection kit package.
5. **Place** FedEx billable stamp on the collection kit package and **call** 1-800-GoFedEx to schedule a pick up.

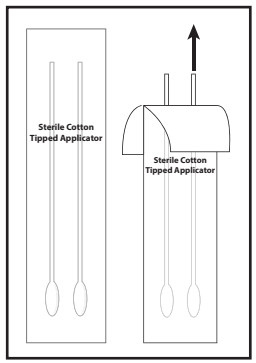


figure 1

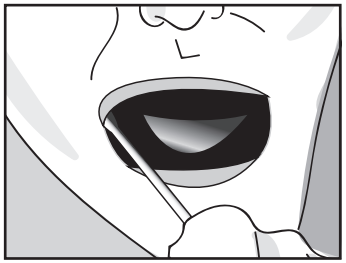


figure 2

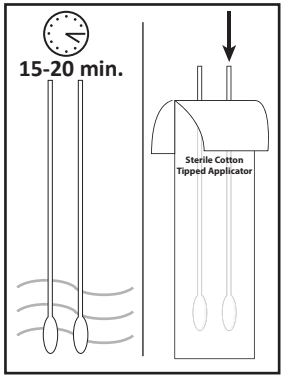
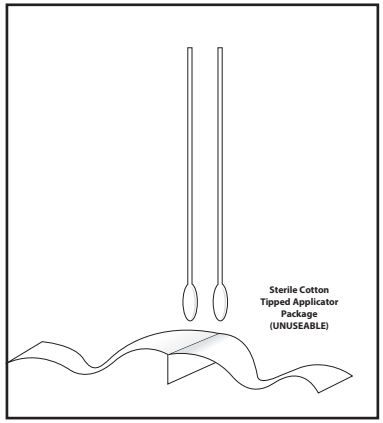


figure 3A figure 3B

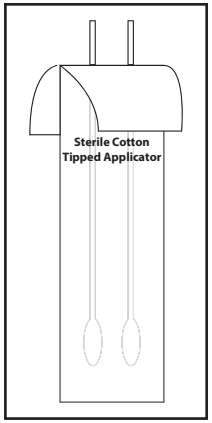
**(REPEAT FIGURES 1 - 3)**

**NO**



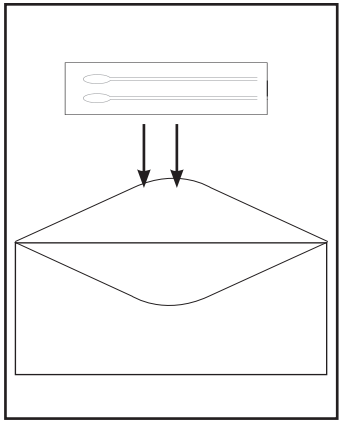
**Package NOT intact**
**SPECIMEN UNUSABLE!!**

**YES**



**Package Intact**
**Specimen Usable**

**YES**


**Insert Specimens into Letter Envelope**