

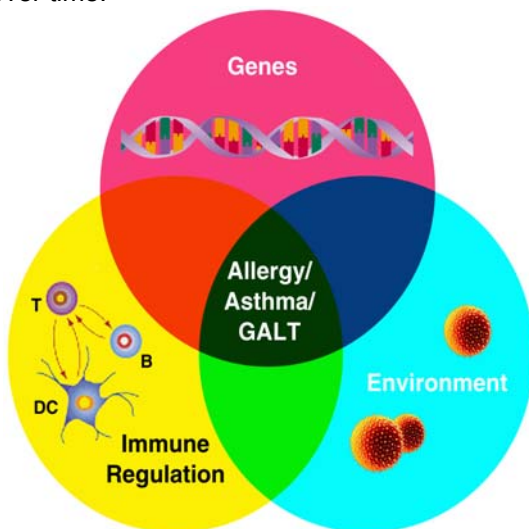
Predictive Genomics for Personalized Medicine

Your Genovations™ Immuno Genomic Profile assesses genomic variations that can influence your health. More than 99% of the human DNA sequence is the same in all humans. Yet the relatively small amount of DNA that differs from person to person is very important. A gene sequence that varies from the usual pattern (a polymorphism) can alter the normal shape and function of proteins. This can change the way your body functions. It can also make you more susceptible to some diseases and more resistant to others.

If you have a genetic variation that makes you susceptible to a certain disease, like an immune-related disorder, it does not mean that you will necessarily develop that specific disease. That's because your genes are fluid and flexible in how they "express" themselves.

Genes, The Environment and Your Health

In almost all cases, a gene's ability to promote disease depends heavily on its being switched "on" or "off" by factors in the environment. These factors can be things like cigarette smoke, air pollution, excessive alcohol consumption, poor diet, sun exposure, irregular sleep patterns, bacterial infection, chronic nutrient deficiencies, hormone imbalances, lifestyle habits or toxic exposure. In other words, the vast majority of genetic polymorphisms only have the potential to cause health problems, if exposed to the wrong "mix" of harmful agents over time.



ImmunoGenomic™ Profile Personalized for

SAMPLE PATIENT

This is particularly true for immune-related disorders, some of the most common and disabling chronic diseases that develop as we age. Health conditions are not caused by genes alone. Instead, they develop when many potentially harmful factors—both genetic and environmental—interact over a long period of time.

Only by considering all of these factors together can a person accurately estimate his or her unique health risks and take the right steps to help prevent chronic disease from developing.

Your Genes are Unique

The most common genomic variations measured in your Genovations™ profile are called single nucleotide polymorphisms, or SNPs (pronounced "Snips") for short.

SNPs are variations in the genetic code that occur only at certain places on your chromosomes. Everyone has SNPs — that's what makes us different from one another. Some SNPs are quite common and others are quite rare. Many SNPs have no effect on our health, but others can predispose us to disease or influence our response to a food or drug.



The SNPs in this profile were carefully selected. Your profile will not measure any SNPs that will absolutely lead to problems with your immune system. Your profile will evaluate only SNPs that may lead to health problems when influenced by other external factors—factors that you can change.



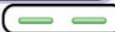



It's very important to remember that the SNPs included on your profile indicate your risk of immunologic conditions, not certainty. Testing positive for a SNP doesn't mean you are sure to develop a specific health problem. By the same token, if you don't have a SNP associated with a certain disease, that doesn't mean you are completely protected from that disease, or that you shouldn't take steps to optimize your health. It just means that your genetic risk is lower for that disease.

The field of predictive genomics continues to evolve. Additional SNPs related to immune system risk could (and probably will) be discovered. It is therefore possible that in the future additional genomic diagnostics will become available to help you further understand your modifiable risk factors related to immune activity.

Understanding Your Genovations™ Profile

The result for each genetic polymorphism is presented graphically on your report. Learning how the information is presented can help you to understand more about your unique genetic makeup. Each gene controls a specific protein/enzyme associated with immune activity, which is noted in bold print.



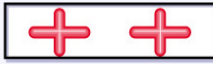
How to read your Genomic Profile

SNP 1	Protein Name
Chromosome 12	Gene Location
677G-A	Polymorphism Location
	Composite Result
	
CATG[G→A]GGAC	SNP Variance (highlighted)
Locus 1 	Multiple SNP addresses (if applicable)
Locus 2 	
Locus 3 	
Locus 4 	

The location of that gene and polymorphism is also noted. The composite result (which will be explained in a moment) is also listed. The variance in the genetic code that is being tested is listed as a genetic sequence of letters, with your potential SNP noted as the letters highlighted in red. In situations where there are more than one location for a polymorphism on a particular gene, multiple SNP addresses are offered, as well as the results for each SNP location. Each genetic polymorphism affecting a specific protein/enzyme can exist on one or both of your genes.

Therefore **composite results** are reported as one of three variations as follows:

Composite Result

	Homozygous negative or wild type, indicating that neither chromosome carries the polymorphism
	Heterozygous positive, indicating that one chromosome carries the polymorphism.
	Homozygous positive, indicating that both chromosomes carry the polymorphism.

Written commentary for each protein/enzyme is also offered. It describes the function of each protein/enzyme assessed, the health implications of your result, how to minimize your risks and further considerations for monitoring your genetic expression.

HEALTH IMPLICATIONS: Interleukin-1 receptor antagonist (IL-1RA) is a naturally induced pro-inflammatory activity. A defect in the IL-1RA gene can contribute to immune response and has been associated with increased risk for chronic inflammatory diseases such as rheumatoid arthritis, lupus, colitis, and Crohn's disease. However, the IL-1RA gene can also protect against cancer through amplified immune vigilance.

MINIMIZING RISKS: Eat a diet rich in anti-oxidants (colorful fruits and vegetables, salmon, and reduce intake of vegetable oil and fatty meat. Fish oil supplementation, silymarin (milk thistle) directly inhibit IL-1 production. Botanicals like boswellia (frankincense), glycyrrhiza (licorice), and curcumin (turmeric) also inhibit IL-1. Compounds in some herbs have also been shown to suppress IL-1. Corticosteroids and cyclosporin A inhibit IL-1 production but with significant immunosuppressive effects. Experimental IL-1RA therapy is showing promise in treating rheumatoid arthritis.

FURTHER EVALUATION: IL-1RA defects lead to increased inflammatory tendencies. Consider evaluation of cardiovascular health (lipids, C-reactive protein, etc.), for bone health (bone density, etc.), for gut health (bowel microbiology, food antibodies, etc.). The physician should be consulted for immune in this patient.

The end of this report contains a summary section of action steps you should consider to optimize your genomic potential related to immune system activity. Based on your genetic test results, your healthcare practitioner can work with you to develop a customized treatment plan. Testing is also available that can monitor whether your personal healthcare strategy is having a positive impact on your genetic risks. These tests, called "functional assessments," give your healthcare provider a concrete way to evaluate how your body is responding to treatment. This is an important way to ensure that powerful environmental factors, such as hormones and nutrients, are in a state of optimal balance that minimizes your in-born genetic health risks.



Patient: **SAMPLE
PATIENT**

DOB:

Sex:

MRN:

Immuno Genomic Profile Results

This profile identifies genetic single nucleotide polymorphisms associated with increased risk of developing defects in immune competence and surveillance. Immune system polymorphisms have been associated with increased risk of asthma, atopy, osteopenia, arthritis, heart disease, auto-immunity and infectious diseases.

Chronic Inflammation

IL-1 β : Interleukin 1-beta, produced mainly by blood monocytes, mediates the panoply of host inflammatory reactions collectively known as acute phase response. Polymorphisms in IL-1 β may predispose individuals to chronic inflammatory conditions by upregulating COX2 activity and prostaglandin production. Other effects include hypochlorhydria, predisposition to H. pylori infection and gastric cancer.

TH-1 Cytokine (Viral Infection & Cancer)

Tumor necrosis factor-alpha (TNF- α) is a pro-inflammatory cytokine that is secreted from activated macrophages. TNF- α plays an important role in host defense against infection; however, excessive release of the cytokine increases inflammation and oxidative stress.

TH-2 Cytokines (Allergy, Asthma & Atopy)

IL-4: Polymorphisms in Interleukin-4 lead to increased IL-4 production and to decreased barrier function in lung epithelial cells causing a hyper-responsiveness to antigen stimulus, leading to increased risk and severity of bronchial asthma.

IL-6: Interleukin-6 contributes to inflammatory response and also affects adipose tissue metabolism, lipoprotein lipase activity, and hepatic triglyceride secretion. This particular SNP has been associated with elevations in serum triglycerides in response to carbohydrate intake and decreased levels of HDL cholesterol.

IL-10: Interleukin-10 has an inhibitory effect on TH-1 cytokine production. Polymorphisms in IL-10 may affect the risk of frequent viral infections, cancer and auto-immune diseases such as rheumatoid arthritis or lupus (SLE).

IL-13: Interleukin-13 acts to promote IgE synthesis and IgE-based mucosal inflammation typical of atopy and bronchial asthma. These SNPs are associated with increased IL-13 production and activity.

Immune Markers

Chronic Inflammation

IL-1 β



TH-1 Cytokine

TNF- α



TH-2 Cytokines

IL-4



IL-6



IL-10



IL-13



Chronic Inflammation

IL-1 β

Chromosome 2
-31C-T



AAGC[C→T]ATAA

Health Implications: Interleukin-1 β , produced mainly by blood monocytes, is an inflammatory cytokine that can inhibit acid secretion in the stomach and stimulate bone resorption. This polymorphism increases IL-1 β production, leading to increased inflammation. Increased IL-1 β has also been shown to suppress hydrochloric acid secretion in the stomach, as well as increase susceptibility to *Helicobacter pylori* infection, gastritis and gastric cancer in *H. pylori*-infected individuals, and liver cancer in individuals with hepatitis C. This genotype may provide some protection against breast and lung cancer and GERD.

Clinical Management Considerations: If *H. pylori* infection is present, eradication and mucosal repair are essential. Once repaired, regular betaine hydrochloride with meals may be warranted to prevent re-infection. Risk of atrophic gastritis and infection may be diminished by reduced alcohol consumption, avoiding smoking, and regularly ingesting fruit. Be careful with all NSAIDs, which reduce gastric blood flow and increase IL-1 β . Production of IL-1 β is suppressed by agents such as fish oils, L-glutamine, milk thistle (silymarin), curcumin, boswellia, ginkgo biloba, and resveratrol.

TH-1 Cytokine (Viral Infection & Cancer)

TNF- α

Chromosome 6
-308G-A



CATG [G→A] GGAC

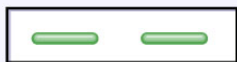
Health Implications: The TNF- α (-) genotype is associated with decreased production of TNF- α , decreased inflammatory tendency and oxidative stress compared to the other genotypes; reduced risk of various autoimmune diseases or their severity; less risk of insulin resistance, obesity, and some cancers (including non-Hodgkin's lymphoma, cervical CA, liver CA, and oral squamous cell CA); reduced risk of asthma or irritant contact dermatitis; less chance of developing sepsis following severe trauma. However, this genotypic result is associated with possible *increased* risks of ischemic stroke in adults (esp. Asians), depression or bipolar disorder, and multiple sclerosis (studies are mixed).

Clinical Management Considerations: No particular treatment is indicated for this result; however, individuals with this result should be encouraged to maintain a healthy lifestyle to minimize inflammation. Individuals with this finding also generally have a positive therapeutic response to anti-TNF- α medications (e.g., etanercept) in rheumatoid arthritis.

TH-2 Cytokine (Allergy, Asthma, & Atopy)

IL-4

Chromosome 2
-590C-T



TTGT [C→T] CCCC

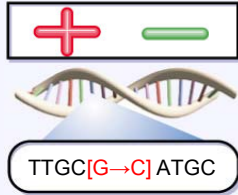
Health Implications: Interleukin-4 is secreted by antigen presenting cells (e.g., macrophages and dendritic cells) and stimulates the differentiation of TH-2 cells and the increased production of IgE. Homozygous negative individuals for the IL-4 polymorphism have lower circulating levels of IgE and are at reduced risk for developing eczema, atopy, or asthma.

Clinical Management Considerations: None recommended for this polymorphism.

TH-2 Cytokine (Allergy, Asthma & Atopy)

IL-6

Chromosome 7
-174G-C



Health Implications: Excess interleukin-6 inhibits lipoprotein lipase and stimulates hepatic triglyceride secretion. This polymorphism of IL-6 is associated with elevated plasma triglycerides, decreased HDL cholesterol, and increased fasting serum glucose. Thus the risk of developing heart disease and adult-onset diabetes is increased substantially with this polymorphism.

Clinical Management Considerations: Since carbohydrates are the primary macronutrient stimulus for triglyceride synthesis, a lower carbohydrate diet with the elimination of simple carbohydrates is indicated. However, since excess IL-6 also impairs lipoprotein lipase activity, a low-fat diet is also indicated. Optimally a low-calorie, higher protein, lower carbohydrate, low-fat diet may be optimal. Fish oil supplementation has also been shown to decrease triglyceride levels.

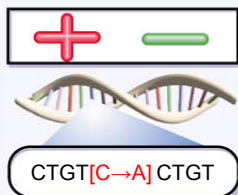
Chronic stress increases concentrations of IL-6 in all individuals, thus, stress reduction and regulation may prove beneficial. Adequate sleep and regular aerobic exercise reduce stress response. Supplements that improve adrenal function and balance include vitamins C and B5, glycyrrhiza (licorice), and adaptogens like the various ginsengs, cordyceps, bacopa and ashwaganda (withania).

Both melatonin and beta-sitosterols from pine trees have been shown to decrease IL-6 production dramatically, reducing inflammatory tendency and improving cell mediated immunity.

TH-2 Cytokine (Allergy, Asthma & Atopy)

IL-10

Chromosome 1
-627C-A



Health Implications: Interleukin-10 is a predominately anti-inflammatory cytokine. IL-10 inhibits the synthesis of other, pro-inflammatory interleukins and acts synergistically with glucocorticoids to reduce inflammation. This polymorphism is associated with reduced secretion of IL-10 and therefore with greater tendency toward chronic inflammation including atherosclerosis, rheumatoid arthritis, inflammatory bowel disease, psoriasis, etc.

Clinical Management Considerations: Therapies that reduce pro-inflammatory stimuli and that inhibit the acute-phase response may be beneficial. Specifically, regular consumption of cold water fish or supplementation with fish oils may reduce tendency to inflammation. Specific anti-inflammatories like boswellia, curcumin, quercetin, hesperedin, ginger, etc. may reduce inflammation, especially during acute inflammatory reactions.

Since IL-10 works synergistically with glucocorticoids, optimizing adrenal function may be helpful. Glycyrrhiza (licorice) has a well-documented glucocorticoid effect, with few of the side-effects associated with steroid use. Vitamins C and B5, as well as ashwaganda (withania) and the ginsengs may optimize adrenal responsiveness.

TH-2 Cytokine (Allergy, Asthma & Atopy)

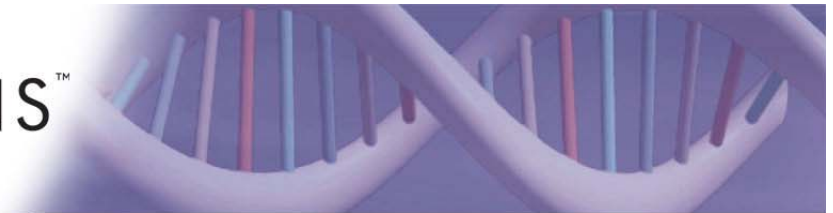
IL-13

Chromosome 5
R130Q



Health Implications: Interleukin-13 stimulates inflammation in the airways and is required for the progression of hyper-responsiveness of airways to antigens leading to symptomatic asthma. The homozygous negative wild-type has normal serum IL-13 concentrations and has no increased risk for developing atopy and asthma. Polymorphisms in IL-4 are also known to play a role in developing asthma and atopy. These are measured elsewhere in this profile.

Clinical Management Considerations: None indicated for this polymorphism.



Optimizing your Genomic Potential

This test has been developed and its performance characteristics determined by Genova Diagnostics, Inc. It has not been cleared 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 the patient's test indicate genetic predisposition that could affect physiologic function and risk of disease. We do not measure every possible genetic variation. The patient may have additional risk that is not measured by this test. Negative findings do not imply that the 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%.



Optimizing your Genomic Potential

What is Inflammation?

Inflammation is the primary means by which the body repairs cells and tissues that have been damaged. Inflammation also is the primary defense mechanism of our immune system fighting against a hostile environment that includes allergens, viruses, bacteria, yeast, etc. Cytokines are a class of polypeptide chemical compounds within the body that regulate both types of inflammation response. Interleukins are a specific subset of cytokines produced by white blood cells. Specific cytokines and interleukins can be either pro-inflammatory or anti-inflammatory. While a certain level of cytokines is always present in the blood, increased cytokine production can result from external stimulus (e.g., pollen or physical injury) but cytokine levels may also vary based on genetic polymorphisms. Increased production of a pro-inflammatory cytokine or decreased production of an anti-inflammatory cytokine can both result in chronic inflammatory conditions.

Your Body's Immune System

The body's immune system may be broadly divided into two major functional categories: cell-mediated immunity (a.k.a. TH-1 immunity) that protects against viral infections and cancer; and humoral immunity (a.k.a. TH-2 immunity) that controls allergic response and antibody formation. These two branches of the immune system are mildly antagonistic: if one is up-regulated, the other is often down-regulated and vice-versa.

Immune-related Illnesses

Imbalanced cell-mediated immunity can lead to frequent infections and to increased risk of developing certain cancers. Imbalanced humoral immunity can contribute to the development of allergy, asthma, atopy, eczema, inflammatory bowel disease, autoimmune disease, osteoporosis, and even atherosclerosis and heart disease. It is important for our long-term health to maintain balance in our immune response. We need adequate inflammation to ensure environmental defense and tissue repair, but without excess inflammation that can cause substantial cellular damage and numerous disease states.






Optimizing your Genomic Potential

Personalized Recommendations for Minimizing Risk

Diet



This section offers **dietary supplementation** considerations based on your unique genetic makeup. These are provided for educational purposes only and are not intended to diagnose or to treat any specific condition. Please consult with your healthcare practitioner for specific interpretation and therapeutic options.

-  Eat a diet rich in colorful fruits and vegetables as these are not only high in mineral content but also the primary source of dietary anti-oxidants, essential for minimizing inflammation.
-  A diet that is lower in total calories, lower in carbohydrates and higher in protein may be best suited for your genetic constitution.
-  Increased consumption of cold water fish and/or the consumption of fish oils should be considered in reducing the overall tendency toward inflammation.

Lifestyle / Environment



This section offers **lifestyle/environment** considerations based on your unique genetic makeup. These are provided for educational purposes only and are not intended to diagnose or to treat any specific condition. Please consult with your healthcare practitioner for specific interpretation and therapeutic options.









Optimizing your Genomic Potential

Nutritional Supplementation




This section offers **nutritional supplementation** considerations based on your unique genetic makeup. These are provided for educational purposes only and are not intended to diagnose or to treat any specific condition. Please consult with your healthcare practitioner for specific interpretation and therapeutic options.

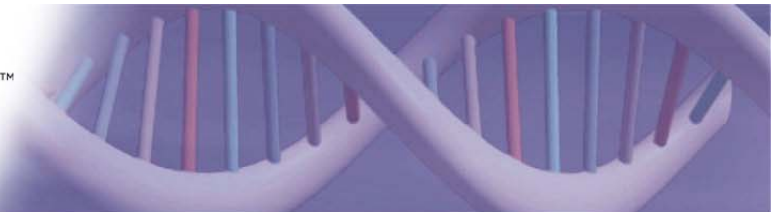
-  Betaine hydrochloride and deglycyrrhizinized licorice (DGL) should be considered to improve stomach HCl and mucous production. HCl should only be administered after gastric ulcers are ruled out. Long-term therapy may be needed.
-  Fish oils and milk thistle have been shown to suppress interleukin production directly, which in part accounts for their anti-inflammatory actions in the body.
-  If signs and symptoms of chronic inflammation are present, consider the use of botanical anti-inflammatories like boswellia (frankincense), glycyrrhiza (licorice), ginger, hesperedin and curcumin (tumeric).
-  Beta-sitosterols and beta-sitosterol glycosides extracted from pine trees have been shown to reduce IL-6 production.
-  Botanical support of adrenal function and stress reduction should be considered. Herbs to consider include ashwaganda, bacopa, cordycaps, licorice and American, Korean or Siberian ginseng.
-  Licorice, because of its glucocorticoid-like activity may be well suited for your genotype to minimize inflammatory tendencies.

Pharmaceutical Considerations



This section offers **pharmaceutical considerations** based on your unique genetic makeup. These are provided for educational purposes only and are not intended to diagnose or to treat any specific condition. Please consult with your healthcare practitioner for specific interpretation and therapeutic options.

-  If signs and symptoms of acute or uncontrolled inflammation are present, consider the short-term use of corticosteroids like cortisol or prednisone.










Optimizing your Genomic Potential

Genomic/Functional Laboratory Testing



This section offers **genomic/functional laboratory testing** considerations based on your unique genetic makeup. These are provided for educational purposes only and are not intended to diagnose or to treat any specific condition. Please consult with your healthcare practitioner for specific interpretation and therapeutic options.

-  This individual has polymorphisms that increase his or her risk of developing heart disease. A full CardioGenomic profile may reveal more personalized therapeutics as a preventative strategy.
-  This individual may have polymorphisms that increase his or her risk of increased bone resorption and of developing osteopenia and osteoporosis. A full OsteoGenomic profile may reveal more personalized therapeutics as a preventative strategy.
-  IL-1B polymorphisms are associated with H. pylori infection and gastric ulcers; screening for serum H. pylori antibodies is recommended, especially if signs and symptoms of ulcers are present.
-  A bone resorption profile to assess the rate at which bone is being lost is indicated. This test may be run sequentially to assess effectiveness of your therapeutic protocol. A baseline bone density scan may also be indicated.
-  Markers present on your profile suggest the potential for chronic inflammation that may increase risk of developing heart disease. A comprehensive cardiovascular assessment should be considered to evaluate functional risk.
-  A metabolic dysglycemia profile including fasting and 2-hour insulin and glucose should be considered, especially if the waist-to-hip ratio is increased to >1.0 for men or >0.8 for women.
-  An adrenal stress profile may be warranted to assess your functional capacity for stress adaptation and response.