OsteoGenomic™ Profile Results
This profile identifies genetic single nucleotide polymorphisms associated with increased risk of developing osteopenia and osteoporosis. Risk factors include impaired collagen synthesis, calcium metabolism, vitamin D3 activity, osteoclast activity and chronic inflammation.

Bone Formation
COL1A1: Collagen 1,α1 is the primary protein matrix used for bone synthesis. Polymorphisms in COL1A1 lead to mildly aberrant collagen formation that can lead to reduced bone mineral density and increased risk of osteoporosis.

CALCR: The calcitonin receptor mediates the cellular action of the hormone calcitonin. Calcitonin acts to decrease serum calcium levels by decreasing osteoclast activity and preventing bone resorption. Polymorphisms in CALCR can lead to decreased bone density.

VDR: Vitamin D3 receptors mediate the actions of vitamin D3 including increased absorption of calcium from the gut, increased osteoblast activity and mineralization of bone. Polymorphisms in VDR can inhibit calcium absorption and decrease bone mineralization.

Bone Resorption/Inflammation
IL-6: Interleukin-6 is a cytokine that participates in the production of osteoclasts and potentiates bone resorption by other cytokines. Although a polymorphism appears to be associated with increased IL-6 production during acute inflammation, several studies have associated the SNP with reduced baseline IL-6 production and less risk of bone loss. IL-6 production increases when estrogen levels decline due to menopause or other factors.

TNF-alpha (TNF-α): Tumor necrosis factor-alpha is a pro-inflammatory cytokine that can contribute to arthritis, asthma, and osteoporosis. Polymorphisms of TNF-α inappropriately activate inflammatory response and increase TNF-α production.

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.
**Bone Formation**

**COL1A1**  
Chromosome 17  
2046G-T

Health Implications: Collagen type 1, alpha-1 is the primary collagen matrix used for bone synthesis. COL1A1 polymorphisms have been associated with reduced bone mineral density (BMD) and increased prevalence of osteoporosis with increased risk of osteoporotic fracture. There appears to be a continuum of bone density depending on genotype: homozygous negatives (- -) have the greatest bone density; heterozygotes (+ -) have less bone density, and homozygous positives (+ +) have the least bone density.

Minimizing Risks: Individuals who are homozygous negative (- -) for COL1A1 have higher bone densities than those with COL1A1 SNPs. However, adequate dietary intake of calcium, phosphorus, magnesium, vitamin D and other bone nutrients should be maintained. Regular weight-bearing exercise has also been shown to optimize bone health.

Further Evaluation: While this COL1A1 genotype is associated with higher bone density, and decreased risk of osteoporosis and bone fracture, nonetheless, regular laboratory evaluation of bone resorption (deoxypyridinoline) should be used to monitor functional risk as well as therapeutic effectiveness of treatment protocols. Bone density scans every 3-5 years should also be considered for individuals over the age of 45.

www.genovations.com/gocol1a

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**Bone Formation**

**CALCR**  
Chromosome 7  
P463L

Health Implications: The calcitonin receptor allows for the cellular actions of the thyroid hormone calcitonin. Calcitonin acts to decrease blood calcium levels by decreasing the bone resorbing activity of osteoclasts and by decreasing the formation of new osteoclasts. Calcitonin, then, is protective against osteopenia and osteoporosis. Persons who are heterozygous (+ -) for CALCR have been shown to have higher bone density and decreased fracture risk than those who are homozygous negative or homozygous positive (- - or + +).

Minimizing Risks: While no clinical intervention trials have yet been performed with CALCR polymorphisms per se, physiologic inference would suggest that persons who are homozygous (either positive or negative) should adopt dietary and lifestyle habits that maximize bone formation. Adequate dietary calcium and magnesium (dairy products, dark leafy greens, seeds, broccoli and bok choi), moderate sunlight exposure or vitamin D supplementation, and weight-bearing exercise have all been shown to optimize bone formation and reduce the risk of osteoporosis. While CALCR heterozygotes have comparatively higher bone density, good dietary and lifestyle habits are essential to maximize genetic potential.

Salmon calcitonin and human recombinant calcitonin are available as a nasal spray and have been shown to be roughly as effective as estrogen replacement therapy in post-menopausal women. The effects of both calcitonin and estrogen therapy are dramatically enhanced (~3-fold) with calcium supplementation.

Further Evaluation: Regular laboratory evaluation of bone resorption (deoxypyridinoline) should be employed to monitor functional risk as well as therapeutic effectiveness of treatment protocols, regardless of genotype. Bone density scans every 3-5 years should also be considered.

www.genovations.com/gocalcr

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**Bone Formation**

**VDR**  
Chromosome 12  
BsmI RFLP

Health Implications: Vitamin D receptors bind active vitamin D [1,25(OH)2D3] and initiate a cascade of biologic effects at the cellular level increasing calcium and phosphorus absorption from the small intestine and stimulating osteoblast activity and bone mineralization. Defects in the VDR gene may lead to reduced peak bone mass as a young adult and to a more rapid decline in bone density after middle age. Vitamin D also stimulates cell differentiation but impedes cell proliferation, and VDR polymorphisms are associated with increased incidence of psoriasis and prostate cancer.

Minimizing Risks: All VDR genotypes have shown increased bone formation with increased exercise and calcium supplementation, however, those with defects in the VDR gene do not respond well to vitamin D supplementation. Calcium supplementation substantially above the DRI (RDA) of 1000-1500 mg/d may be warranted.

Because absorption of calcium may be impaired, dietary factors that increase calcium excretion should be avoided: excess caffeine, tobacco, phosphorus, sodium, and protein. Improving insulin sensitivity and supplementing with chromium picolinate have been shown to reduce the urinary excretion of calcium and hydroxyproline in post-menopausal women, and may provide a novel therapeutic approach.

Plant-based phyto-estrogens (black cohosh, soy isoflavones, etc.) and estrogen replacement therapies have been shown to reduce bone resorption in post-menopausal women.

Further Evaluation: This VDR genotype is associated with lower bone density, decreased calcium absorption and utilization, and increased bone resorption at all ages. Accordingly, regular laboratory evaluation of bone resorption (deoxypyridinoline) should be employed to monitor therapeutic effectiveness. Bone density scans every 3-5 years should also be considered. Insulin resistance syndrome should be ruled out via a metabolic dysglycemia analysis. Regular screening for prostate health in men may also be advisable.

www.genovations.com/govdr
Bone Resorption/Inflammation

**IL-6**
Chromosome 7
-174G-C

[Image of TTGC[G→C] ATGC]

**HEALTH IMPLICATIONS:** IL-6 is a cytokine that, along with other cytokines, participates in the production of osteoclasts, the cells responsible for bone resorption. Although IL-6 is not considered a powerful direct stimulator of bone resorption, it can dramatically potentiate bone resorption by other cytokines. A polymorphism in IL-6 (represented by a (+) sign on the report) is generally associated with reduced baseline plasma IL-6 levels. However, the SNP appears to be associated with temporary increases in IL-6 production in cases of acute inflammation. A homozygous positive (++) genotype is associated with less bone resorption and greater bone mineral density as compared with other genotypes. Because of the lower IL-6 levels associated with the polymorphism, homozygous positive individuals are also less prone to chronic inflammatory conditions such as peripheral arteriosclerosis and clinical progression in autoimmune diseases.

**MINIMIZING RISKS:** None indicated for the homozygous positive genotype, other than avoidance of acute inflammatory stressors that may trigger temporary spikes in IL-6.

**FURTHER EVALUATION:** None indicated for this genotype.

Bone Resorption/Inflammation

**TNF-α**
Chromosome 6
-308G-A

[Image of CATG [G→A] GGAC]

**HEALTH IMPLICATIONS:** Tumor necrosis factor, alpha (TNF-α) is a pro-inflammatory cytokine secreted from activated macrophages, which plays an important role in host defense against infection. Excessive TNF-α release can result in inflammatory reactions, one of the common contributors to bone loss. A homozygous negative (– –) genotype is associated with decreased production of TNF-α, consequently decreased inflammatory tendency and oxidative stress. Risk is reduced for osteoporosis, autoimmune disease, and insulin resistance, but may also be associated with an increased risk of some cancers because of TNF-α's anti-neoplastic properties.

**MINIMIZING RISKS:** Risk of inflammatory disorders is minimal. A diet and lifestyle associated with minimizing cancer risks is still prudent, including a diet rich in vegetables, fruits, and fiber, and properly balanced in essential fatty acids. Avoid smoking and minimize exposure to environmental pollution and toxins.

**FURTHER EVALUATION:** None indicated for this polymorphism.
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 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.
Bone Health

While bone health is important in providing structure to our bodies, the minerals in bone like calcium, phosphorus, and magnesium serve even more critical functions in maintaining health. Known as electrolytes, these minerals are essential for virtually all human physiology, including nerve conduction, muscle contraction, cell membrane function, and so on. Our bones provide a metabolic reservoir of these minerals. When we don't get enough of these minerals in the diet or for whatever reason can't absorb adequate amounts, our bones suffer. In fact, the body will sacrifice its bone in order to maintain normal serum levels of these important minerals, especially calcium. The body has developed many hormonal controls to ensure that serum calcium is maintained, even if that means sacrificing bone quality to do it.

Calcium Metabolism

If serum calcium levels fall, the parathyroid gland secretes parathyroid hormone (PTH) that binds to receptors stimulating the production and release of active vitamin D that in turn stimulates increased absorption of calcium and phosphorus in the intestine as well as increased kidney resorption of calcium from the urine. PTH also stimulates osteoclasts to break down, or "resorb" bone, releasing its calcium into the blood stream.

Calcitonin, a hormone secreted by the thyroid gland, shuts down osteoclast activity in the bone and thus prevents bone resorption and lowers serum calcium. Calcitonin and parathyroid hormone act in opposite directions allowing the body to raise low serum calcium levels as well as lower high serum calcium levels. The actions of both hormones working together permit serum calcium levels to remain balanced.

Bone is not just calcium, however. In fact, bone is a mineralized protein, type-1 collagen. If collagen synthesis is impaired, bone formation will lag and we may also suffer from bone disorders like osteoporosis.

Chronic inflammation can also act to increase bone resorption. Pro-inflammatory cytokines, such as TNF-?, IL-1 and IL-6, directly and indirectly influence the production and lifespan of osteoclasts, the cells responsible for bone resorption. Pro-inflammatory cytokines, in fact, are among the most powerful stimulants of bone resorption known. High levels of cortisol, secreted during stress, can also contribute to bone resorption.

Every step of this process: maintaining serum calcium levels, bone formation, bone resorption, hormone production and action is controlled by the interaction of our genes and our environment.

Minimizing Your Risk

The following pages summarize dietary, lifestyle, supplemental, and prescription interventions based on your unique genetic makeup that will help maximize your genetic potential to maintain healthy bones and lower your risk of developing osteoporosis. Functional genomic testing only reveals your predisposition to a particular condition. All of the genes identified in functional genomic testing are modifiable based on your environment and how you choose to live. Functional laboratory tests can be used to evaluate the functional integrity of your bones and to monitor the therapeutic effectiveness of any treatment regimen you and your health care practitioner decide to follow. Suggestions of useful functional laboratory tests are included, as are suggestions for other potentially useful genomic tests. With the help of genomic and functional laboratory testing your practitioner can develop a treatment protocol that is specific to your unique needs. Following that treatment plan and maximizing your genetic potential is up to you.
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.

- Eat foods that are high in calcium. Excellent food sources of calcium include dairy products, dark leafy greens, broccoli, bok choy and seeds.

- Eat foods that are high in magnesium. Excellent food sources of magnesium include all green foods, nuts, and seeds.

- Avoid overconsumption of caffeine, soda or pop, sodium or salt, and excess protein as these have been shown to increase calcium excretion.

**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.

- Regular, moderate, weight-bearing exercise stimulates bone formation. Walking, running, and weight training are excellent forms of weight-bearing exercise.

- Do not smoke. Tobacco use has been shown to increase calcium excretion in the urine which could be very detrimental to a person with your genotype.
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.

- Additional supplemental calcium and magnesium may prove beneficial over and above what is achievable in the diet.
- Cod liver oil or purified fish oils containing EPA and DHA may be useful in reducing inflammation and increased bone resorption.

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.

- Estrogen or hormone replacement therapy should be considered in cases refractory to other forms of intervention when bone resorption markers (e.g., deoxypyridinoline) remain elevated. Estrogen's effects on preventing bone resorption is enhanced by using supplemental calcium.
- Calcitonin therapy is comparable in effectiveness to estrogen replacement in post-menopausal women at reducing the rate of bone resorption. Calcitonin therapy provides a useful alternative to women who cannot or do not want to use estrogen replacement therapy, and also for men, for whom estrogen therapy is not appropriate. Calcitonin's effects on preventing bone resorption is enhanced by using supplemental calcium.
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.

- Increased inflammation increases the risk of atherosclerosis and cardiovascular disease. A full evaluation of genomic markers for immune dysfunction and cardiovascular dysfunction should be considered.

- Bone resorption is a sensitive marker of osteoporotic fracture risk along with bone density. A bone resorption test measures markers of bone protein resorption: deoxypyridinoline and pyridinoline. This will help to assess osteoporotic fracture risk, as well as the ongoing effectiveness of any treatment protocol.

- Bone density is the standard by which osteoporosis is diagnosed. Multi-focal bone density analysis is recommended for all individuals over 45 and for all post-menopausal women.

- Increased inflammation tendencies may cause predisposition to cardiovascular disease. A comprehensive analysis of cardiovascular markers including high-sensitivity C-reactive protein, fibrinogen, and triglycerides may be useful.