The Power of Nutrigenomics: A Practical Guide for Application in the Treatment of Chronic Illness

Advances in the understanding of genetics are changing the way healthcare professionals think about disease causes and prevention. It's now accepted that a person's state-of-health arises from the dynamic interaction of environmental factors with his or her genetic uniqueness. And, nutrition has emerged as a primary environmental factor that can positively or negatively impact the extent to which a person will realize his or her genetic potential.

Nutrition research in the past has focused on nutrient deficiencies and impairment of health. But the Human Genome Project has led to the concept of “personalized medicine” not only with drugs (pharmacogenetics), but with nutritional modalities as well. Nutritional genomics—or nutrigenomics—is the “junction between health, diet, and genomics.” In other words, nutrigenomics is the effect that nutritive substances and phytochemicals have on genetic expression within human cells.

As a growing field of research, nutrigenomics is the recognition of the ability to optimize nutrition for maintaining and extending a state of optimal health. This growing field of research has demonstrated the effects that nutrients and botanicals can have on modifying gene expression, prompting the development of research-based nutraceuticals, functional foods, and dietary approaches to address disorders in genetically pre-disposed individuals.

The Future of Health Care...Here Today

New developments in nutrigenomic research are predicted to offer enormous potential for the development of dietary optimization approaches. But you won’t have to wait for therapies applying basic and advanced nutrigenomic principals to benefit the health of your patients. They're already here.

Clinically effective modalities for applying nutrigenomics are already in use in a variety of healthcare practices. Nutrigenomics in clinical practice entails using specified, defined nutrients and nutritional programs to target genetic expression for improved patient outcomes without serious adverse effects. These new, patient-centered approaches to health care rely upon nutrition and other modifiable lifestyle factors to help people achieve optimal genetic expression.
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The Nutrigenomics Matrix

This chart is provided for your reference as a summary of how nutrigenomics can easily be put into practice for the health of your patients. The combination of healthy dietary choices, medical foods, SKRMs, and other targeted nutrients can be a revolutionary avenue of support for those suffering from a number of chronic illnesses.

*This is the power of nutrigenomics.*

<table>
<thead>
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<th>Conditions</th>
<th>Dietary Signal Modification</th>
<th>Medical Food Support</th>
<th>SKRMs</th>
<th>Key Nutritional Support</th>
</tr>
</thead>
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<tr>
<td>Metabolic Syndrome &amp; Cardiovascular Disease (CVD)</td>
<td>FirstLine Therapy&lt;sup&gt;®&lt;/sup&gt;</td>
<td>UltraMeal&lt;sup&gt;®&lt;/sup&gt; PLUS 360° featuring SKRMs</td>
<td>RIAA &amp; Acacia</td>
<td>CoQ&lt;sub&gt;10&lt;/sub&gt; EFAs</td>
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<tr>
<td></td>
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<td>UltraMeal&lt;sup&gt;®&lt;/sup&gt;</td>
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<tr>
<td>Inflammatory Bowel Disease (IBD)</td>
<td>FirstLine Therapy&lt;sup&gt;®&lt;/sup&gt;</td>
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<td>RIAA</td>
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<td>UltraInflamX&lt;sup&gt;®&lt;/sup&gt;</td>
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<td>Type 2 Diabetes</td>
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<td>Silymarin Catechins Artichoke Leaf Watercress Ellagic Acid</td>
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<td>UltraClear PLUS&lt;sup&gt;®&lt;/sup&gt;</td>
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<td>Leaky Gut Syndrome</td>
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The principles of nutrigenomics can be applied easily in any healthcare practice.
3-Phase Plan for Implementing Nutrigenomics

You can easily tailor and prescribe a program for patients presenting with a variety of common and chronic health conditions. A nutrigenomic approach to wellness can include any or all of the following:

1A. Dietary Signal Modification with TLC
Western diets, foods of convenience, and other unhealthy dietary habits can "muddle" the signals sent to cells throughout the body, fostering negative genetic (phenotypic) expression that leads to premature aging and disease. What people eat, therefore, may have a direct influence on how they feel. And addressing those eating patterns allows your patients to manage symptoms and even halt or reverse the progression of their illnesses.

You can help them make informed decisions that impact their health by offering therapeutic lifestyle changes (TLC). TLC can provide food plans that incorporate nutrigenomic principles for a broad population, then further customize these plans based on patient response, individual concerns, and specific nutritional needs.

1B. Dietary Signal Modification with Medical Foods
Medical foods offer an adjunct approach to dietary recommendations to nutritionally manage specific conditions. A medical food is formulated with macro- and micronutrients that are recognized by scientific principles to support the dietary management of a disease or condition, and is to be administered under the supervision of a physician or licensed healthcare practitioner.

Medical foods contain nutrients that typically cannot be acquired through normal dietary measures. Some patients may require a level of nutritional support that simply cannot be met by even a food plan with the best intentions. Medical foods offer a powerful tool, yet can be very simple to implement in your practice.

2. Selective Kinase Response Modulators (SKRMs)
Dietary signals are translated by enzymes known as kinases at the cellular level, helping to direct genetic expression. Selective kinase response modulators—or SKRMs—are nutritional substances that can work to modulate kinase signaling back into balance, helping to restore healthy signaling to genes, favorably affect genetic expression, and reverse the effects of chronic illness.
Where an unhealthy diet makes the kinase signaling unclear, SKRMt help increase the volume of the message for positive genetic expression and preservation or restoration of health. These research-based nutritional substances offer the newest avenue for a natural approach to wellness that embodies the ideals of nutrigenomics.

3. **Targeted Nutritional Support**

Even the most comprehensive approach to wellness may require additional nutritional support for maintaining health, addressing specific symptoms, or customizing approaches for patients with multiple health concerns.

Outlined here are just a few approaches of the hundreds of possibilities for targeted nutritional applications—from additional support for joint protection and restoring healthy gut ecology to maintaining healthy hormone balance and blood sugar levels.
Phase 1A
Changing Primary Dietary Signals with TLC

The first step in a nutrigenomics intervention is changing primary dietary signals. Foods contain nutrients serving as dietary signals that travel to cells throughout the body, where they are translated by kinases. Healthy food choices foster healthy signaling. Poor food choices, however, can trigger a disorder of kinase signaling, resulting in poor genetic expression and, ultimately, chronic illness. In fact, poor nutrition is one of the three leading factors attributed to 70% to 90% of mortalities from chronic illnesses in the U.S. alone.

Prior to the commercialization of the Western diet, humans (over centuries) developed a relationship with commonly eaten foods. Existing in harmony with these foods meant dietary signals that were adequate to maintain health. Changing the diet with commercialized foods and introducing foreign substances creates a state of cellular stress where messages can be distorted and negatively affect physiological function. But these negative dietary signals don’t have to be a part of modern living, nor do the long-term costs of premature aging and chronic disease development.

Figure 1. The nutrients (or lack thereof) and other foreign substances (xenobiotics) in a diet can both directly and indirectly influence genetic expression, impacting health.
How can you help modify your patients’ dietary signals? This can be accomplished through therapeutic lifestyle changes (TLC). Scientific evidence in support of TLC programs as a fundamental therapy for chronic conditions—including cardiovascular disease (CVD), type 2 diabetes, and obesity—continues to grow.\textsuperscript{7,9-21}

An optimal TLC program should include recommendations for exercise for a comprehensive approach. It should also provide the means and flexibility for further personalization of condition-specific support with nutrients that may not be possible to obtain through dietary measures—or difficult to obtain in therapeutic amounts. Medical foods (Phase 1B on page 10) are designed to complement dietary approaches for the nutritional management of specific conditions.

Help for Implementing Dietary Signal Changes

The responsibilities of a patient change in the management of chronic disease. Because the patient takes on a caretaker role in the treatment process, greater educational efforts are needed for successful outcomes.\textsuperscript{\textsuperscript{22,23}} Unfortunately, many practices are set up for acute disease management rather than chronic illness care, and may not be prepared to institute efforts such as lifestyle modification programs.\textsuperscript{23}

\textit{FirstLine Therapy}\textsuperscript{®} is an example of a TLC program that can help healthcare practitioners teach their patients how to adopt dietary changes that can positively affect kinase signaling to support genetic expression, befitting a longer, healthier life.

The \textit{FirstLine Therapy} food plans are based on a traditional Mediterranean-style eating plan that has an overall low glycemic load (for balancing blood sugar), low in arachidonic acids (anti-inflammatory), and high in phytIsnents. Moreover, the foods have been screened for a history of safe use and for unique molecules that have the ability to modulate kinase signaling in a positive manner. These foods affect signal transduction to help increase the clarity of messages sent to kinases, creating a potential to combat chronic disease and restore optimal wellness. A “disordered” physiology will respond to these new signal conductors, reducing the burden of prior unhealthy eating habits.

For optimal support, these dietary changes may be customized—through tailored food plans and medical foods—to meet the specific needs of patients, such as those with conditions related to insulin resistance, cardiovascular disease, autoimmune disorders, inflammatory conditions, fatigue syndromes, and hormone imbalances.
• **Cardiovascular & Insulin Resistance Conditions**

Many conventional dietary programs recommended by leading health organizations are lowfat, high-carbohydrate diets designed to lower elevated cholesterol levels. However, individuals on these diets may eat high-glycemic-index foods that can cause spikes in blood sugar—increasing hunger, decreasing satiety (feeling of fullness), and fostering insulin resistance and a variety of related health problems. Most importantly, these diets may not produce the desired results.\(^{19}\)

Dietary choices causing a high insulin response have been linked to the development of metabolic syndrome, type 2 diabetes, and cardiovascular disease (CVD).\(^{12,24-26}\) Research has demonstrated, for example, that the Western diet—also referred to as the Standard American Diet (SAD)—modulates kinases and insulin signaling.\(^{27}\)

Science-based recommendations include reducing consumption of high-glycemic-index foods (e.g., simple sugars, processed and snack foods) and/or replacing them with low-glycemic-index fruits, vegetables, and whole grains.\(^{12,28-30}\) This also adds fiber for a lower overall glycemic load (GL).\(^{26}\)

A low-GL food plan promotes healthy blood sugar and energy levels in your patients. Research also links insulin resistance to CVD risk (as is the case in metabolic syndrome), making this an appropriate eating plan for cardiovascular disease.\(^{13,19}\) Low-GL diets have also been shown useful in conditions involving inflammation and oxidative stress, reinforcing its application for CVD patients.\(^{21,31}\)

• **Inflammatory, Gastrointestinal, Autoimmune & Fatigue Disorders**

Diet may also represent a significant immune-modulating part of a patient’s environmental exposure. An increasing body of research suggests that chronic or recurring inflammatory disorders may be reactions to substances that trigger an immune response from the gastrointestinal (GI) tract. Dietary changes may have a noticeable impact on modifying the underlying inflammatory signals that are associated with autoimmune disorders. Scientific studies have demonstrated the effectiveness of dietary therapies in alleviating the symptoms and even in altering the progression of inflammatory and autoimmune conditions.\(^{31-49}\)

Research suggests that many common inflammatory and gastrointestinal conditions are triggered by sensitivities or reactions to certain foods and that removing these offending foods may provide relief.\(^{32-49}\) Broad guidelines for eliminating common foods that trigger inflammation can be customized as patients slowly
challenge the reintroduction of foods to determine those that may exacerbate symptoms.

A low-GL diet has also been shown to be beneficial in reducing oxidative stress—the overproduction of damaging free radicals associated with chronic fatigue syndrome and conditions such as rheumatoid arthritis and inflammatory bowel disease (IBD). Low-GL foods that are rich in antioxidants—berries, red grapes, garlic, spinach, whole grains—can help restore the body’s balance of antioxidants and combat harmful free radicals generated by environmental toxins, inflammation, and unhealthy lifestyle habits.

While a modified elimination diet may provide an approach for long-term condition and symptom management, sometimes a more aggressive, non-fasting dietary approach may be warranted. Some symptoms of chronic fatigue syndrome, for example, may be immediately relieved through a liver detoxification program featuring a more aggressive elimination diet for a shorter term.

- **Hormone Imbalances & Cycle–related Symptoms**

  In both men and women, unhealthy diets are one of the many factors that influence the body’s ability to balance hormones. Additionally, foods and beverages can include exogenous sources of hormones that overload the body’s natural ability to detoxify and excrete them.

  Estrogen imbalance in women, for example, may manifest as premenstrual syndrome, irregular menstrual cycles, fibrocystic breast disease, endometriosis, or dysmenorrhea, as well as foster symptoms that impact daily living—hot flashes, night sweats, anxiety attacks, and mood fluctuations.

  Targeted dietary changes—such as the inclusion of cruciferous vegetables and adaptogenic phytoestrogens like soy—can support the body’s production, use, and excretion of various hormones, particularly estrogen. These dietary changes can positively affect the detoxification of circulating estrogens, thereby creating a positive estrogenic influence on activities at the cellular level.
Phase 1B
Changing Primary Dietary Signals with Medical Foods

Food plans and other lifestyle changes may only provide part of the recommendations for changing dietary signals for optimal health support. Medical foods, ever increasing in use, provide an ideal complement to dietary changes to help modify kinase signaling for patients presenting with a variety of conditions, such as those related to dysglycemia and inflammation. Medical foods contain therapeutic levels of nutrients that would be difficult, if not impossible, to achieve through traditional dietary means to support specific conditions.

For almost two decades, Metagenics has been one of the few companies to develop and manufacture medical foods. The genesis of these medical foods was based on burgeoning research now known as nutrigenomics. These medical foods are backed by numerous clinical studies and extensive peer-reviewed scientific support.

For added assurance and developmental research purposes, these medical foods undergo continual testing in a clinical setting at the Functional Medicine Research CenterSM (FMRC), the clinical research arm of Metagenics.

The SKRM Effect: Creating the Next Generation of Medical Foods

Medical Foods with the inclusion of SKRMs offer a multi-mechanistic approach to offer even more opportunities for patient success. They represent the latest in medical food development, incorporating nutrigenomic research and technology for a new degree of health support. (For more information on SKRM research, please see Phase 2—Modulating Kinase Signaling with SKRMs on page 18.)

The following medical foods are intended to complement dietary recommendations to offer nutritional support for the management of specific conditions. Healthcare practitioners, however, are best qualified to decide on a case-by-case basis when other patients may also benefit from the nutrients provided by formulas designed to address:

- Metabolic syndrome
- Cardiovascular disease
- Inflammatory bowel disease (autoimmune support)
- Type 2 diabetes
- Chronic fatigue syndrome (liver detoxification support)
- Premenstrual syndrome (hormone balance)
- Leaky gut syndrome
• **Metabolic Syndrome & Cardiovascular Disease**

*UltraMeal® PLUS 360° Medical Food* is formulated with the addition of SKRMs—in the form of reduced iso-alpha acids (RIAA, from hops) and acacia extract—to complement the formula’s nutritional support for the management of conditions associated with cardiovascular disease and metabolic syndrome. This advanced formula:

- Provides a proprietary soy protein and plant sterol blend that contains 2 grams of plant sterols (including beta-sitosterol) and 15 grams of soy protein per serving. Foods containing at least 0.65 g per serving of plant sterol esters, eaten twice a day with meals for a daily total intake of at least 1.3 g as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease.
- Provides 5-methyl-tetrahydrofolate (5-MTHF)—a body-ready, nature-identical folate—to promote healthy homocysteine levels for cardiovascular health.
- Offers a low-glycemic-index meal option to encourage healthy insulin and blood sugar levels.
- Supplies high quality foundation nutrition for patients with CVD.

In individuals with metabolic syndrome and high cholesterol, this advanced medical food formula and accompanying program has been clinically shown to improve the following important cardiovascular risk factors:56

- Lower the apolipoprotein B–to-apolipoprotein A1 (apoB/ApoA1) ratio
- Reduce total cholesterol, LDL cholesterol, and triglyceride levels
- Increase HDL (“good”) cholesterol levels
- Lower homocysteine levels

(See *Table 1* on the following page for clinical results.)

*Also available without SKRMs as UltraMeal® and UltraMeal® PLUS.*
**Table 1.** The summary of lab value changes from a 12-week, 2-arm study above illustrates the additive affect of a medical food and SKRMs on markers of cardiovascular health. Metabolic outcomes were improved more significantly with a medical food and SKRMs than with a low-GL diet and exercise alone.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Arm 1: UltraMeal PLUS 360° with Low-GL Diet Plan &amp; Exercise</th>
<th>Arm 2: Low-GL Diet Plan &amp; Exercise Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol</td>
<td>-36.74*</td>
<td>-16.33*</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-89.39*</td>
<td>-30.89</td>
</tr>
<tr>
<td>HDL-C</td>
<td>2.65*</td>
<td>1.06</td>
</tr>
<tr>
<td>LDL-C</td>
<td>-28.38*</td>
<td>-15.06*</td>
</tr>
<tr>
<td>TChol/HDL-C</td>
<td>-1.35*</td>
<td>-.61*</td>
</tr>
<tr>
<td>TG/HDL</td>
<td>-3.01*</td>
<td>-1.01</td>
</tr>
<tr>
<td>ApoA1</td>
<td>-4.00</td>
<td>-8.44</td>
</tr>
<tr>
<td>ApoB</td>
<td>-25.70*</td>
<td>-15.06*</td>
</tr>
<tr>
<td>ApoB/ApoA1</td>
<td>-.12*</td>
<td>-.05*</td>
</tr>
</tbody>
</table>

* These results are statistically significant.
• **Inflammatory Bowel Disease (Autoimmune Support)**

    *UltraInflamX<sup>®</sup> PLUS 360°* Medical Food is formulated with SKRMs—in the form of reduced iso-alpha acids (RIAA, from hops)—to complement the formula’s nutritional support for the management of inflammatory bowel disease (IBD), such as Crohn’s disease or ulcerative colitis. This unique medical food:

    • Provides a low-allergenic-potential protein base in the form of rice protein concentrate.
    • Supplies L-glutamine, a valuable energy source for intestinal mucosal cells.
    • Provides ginger and rosemary, which may help support healthy eicosanoid and cytokine metabolism.
    • Supplies generous levels of turmeric extract, which has been shown to inhibit the activity of a wide variety of enzymes, cytokines, eicosanoids, and reactive species implicated in pain and inflammation.
    • Offers an excellent source of antioxidants with a very high oxygen radical absorbance capacity (ORAC) value.

Advantages of the addition of SKRMs include:

• Shown to beneficially influence the function of kinases involved in inflammatory processes.
• Suggested by research to positively influence inflammation-signaling molecules such as NF-κB, COX-2, and PGE<sub>2</sub>.

*Also available without SKRMs as UltraInflamX<sup>®</sup> Medical Food.*
Type 2 Diabetes

UltraGlycemX® Medical Food is formulated to meet the specialized nutritional needs of patients with type 2 diabetes, insulin resistance, and hypoglycemia by providing a low-glycemic-index blend that includes high amylose starch (a resistant starch), targeted plant nutrients from green coffee beans and cinnamon, and heart-healthy soy protein and barley ingredients. UltraGlycemX:

- Supports healthy heart function by providing 15 grams of soy protein per serving. Diets low in saturated fat and cholesterol that include 25 grams of soy protein a day may reduce the risk of heart disease.
- Provides 11 grams of specialized dietary fibers per serving to help maintain healthy blood glucose levels in type 2 diabetics.
- Includes green coffee bean extract (containing chlorogenic acid) and barley beta-glucans for support of healthy glucose, lipid, and insulin metabolism.
- Offers a low-glycemic-index meal option to encourage healthy insulin and blood sugar levels.
- Supplies resistant starch that “resists” digestion and is metabolized much like dietary fiber, with positive implications for glucose and insulin metabolism.
- Provides beneficial levels of cinnamon, chromium, biotin, and magnesium to promote healthy glucose uptake and insulin function.

36% Average Decrease in 2-hr Postprandial Insulin

Figure 2. A preliminary, randomized, 2-arm clinical study of 37 insulin-resistant patients showed a greater average decrease when supplementing with an UltraGlycemX formula.57
• **Chronic Fatigue Syndrome (Liver Detoxification Support)**

*UltraClear® Medical Food* is formulated to provide readily assimilable macronutrients (protein, carbohydrates, and fats) to help address altered energetic function in patients with chronic fatigue syndrome.

- Designed for those patients who may benefit from specific nutritional support for hepatic detoxification function.
- Provides nutrients and antioxidants that support hepatic detoxification processes.
- Provides low-allergenic-potential protein in the form of rice protein concentrate, which may be beneficial during times of increased hepatic detoxification burden.
- The rice protein concentrate has been prepared via a unique process that reduces its already low allergenic potential.

*UltraClear PLUS® Medical Food*

- Provides the same low-allergenic-potential rice protein base and macronutrients, but designed for those patients who may benefit from specific nutritional support for Phase II hepatic detoxification function with the addition of:
  - Glycine to support Phase II glycine conjugation
  - Magnesium sulfate and L-cysteine to support Phase II sulfation
- Also provides green tea catechins and mixed carotenoids to protect against reactive species generated during hepatic detoxification.

*UltraClear® Plus pH Medical Food*

- Provides the same low-allergenic-potential rice protein base and macronutrients, but designed for those patients who may benefit from specific nutritional support to promote alkalinization of urine and Phase II hepatic detoxification function with the addition of:
  - Potassium citrate to promote alkalinization of urine
  - Sesame (a source of sesamin) to help support Phase II hepatic metabolism of lipids (including cholesterol) and other substances
  - Glycine and taurine to support Phase II amino acid conjugation
  - Magnesium sulfate to support Phase II sulfation

Further personalize an approach by identifying those patients with needs for additional detoxification support.
- **Premenstrual Syndrome (PMS)**

*Estrium® Medical Food* is formulated to provide specialized nutritional support for premenstrual syndrome by supplying flaxseed, isoflavones, and targeted nutrients. This targeted formula:

- Supports healthy estrogen metabolism and balance with flaxseed and non-soy isoflavones (from kudzu).
- Supplies generous levels of vitamin E, vitamin B₆, calcium, magnesium, and chromium to address particular concerns associated with PMS.
- Offers a low-glycemic-index meal option to help support healthy energy and insulin metabolism.
- Provides turmeric extract, which has been shown in research to inhibit the activities of a wide variety of enzymes, cytokines, eicosanoids, and reactive species implicated in pain and inflammation.

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**Figure 3.** In a clinical study of 40 PMS patients following the Estrium program for two menstrual cycles there was a significant improvement in symptoms as measured by the Shortened Premenstrual Assessment Form (scores from 10 to 30 indicate symptomatology in the last half of the cycle).³⁹
• **Leaky Gut Syndrome**

*UltraClear SUSTAIN® Medical Food* is formulated to provide specialized nutritional support, including L-glutamine and readily assimilable, low-allergenic-potential macronutrients for patients with leaky gut syndrome.

- Provides L-glutamine, a valuable energy source for intestinal mucosal cells.
- Addresses dysbiosis associated with leaky gut syndrome by providing inulin and fructooligosaccharides (FOS) to promote the growth of healthy intestinal bacteria.
- Provides prebiotic factors, which encourage the production of short-chain fatty acids (SCFAs) that promote intestinal mucosal health and a healthy intestinal environment.
- The rice protein concentrate has been prepared via a unique process that reduces its already low allergenic potential.

**Medical Food Nutritional Profiles & Research**

Nutritional information for the medical foods mentioned in this document is available at [www.metagenics.com](http://www.metagenics.com). In addition to extensive developmental research and clinical studies, these medical foods undergo continual testing in a clinical setting at the Functional Medicine Research Center.

**Phase 2**  
Modulating Kinase Signaling with SKRMs

Nutrigenomic research, such as that conducted by the MetaProteomics® Nutrigenomics Research Center, attempts to discover highly active substances from food and other natural sources that can serve as potent dietary signaling molecules to positively affect genetic expression. Optimally, this yields the development of unique food ingredient extracts from which individual bioactive molecules can be isolated and tested for their ability to modify cellular function related to various disease processes.

Many prevalent health issues have been found to have specific underlying kinase signaling components. This is due to the ability of kinases to translate dietary signals in a positive or negative manner to influence health. For example, research has shown that impaired kinase signaling can lead to impaired insulin response and hyperlipidemia associated with type 2 diabetes.59

Kinases are enzymes that chemically modify other proteins and regulate the majority of cellular pathways—particularly those involved in the transmission of intracellular signals. These enzymes also help regulate eicosanoids, cytokines, reactive oxygen species, and other mediators that may negatively impact the body both locally and systemically.

**Modifying Genetic Expression with SKRMS**

![Diagram](image)

*Figure 4. SKRMs positively affect kinase signaling for optimal genetic and phenotypic expression for wellness. SKRMs are an ideal complement to positive dietary changes for restoration of healthy kinase activities.*
As mentioned previously, SKRMs are nutritional substances that can work to modulate kinase signaling back into balance. This balance helps restore healthy signaling to genes for positive genetic expression and reversal of illness.

Proprietary research has yielded the discovery of food-derived SKRMs that specifically inhibit kinase-mediated processes associated with insulin resistance and inflammation. SKRMs may offer therapeutic advantages over dietary modifications alone.

**Insulin SKRMs**

Groundbreaking preliminary research suggests the identification of SKRMs that have the ability to improve insulin sensitivity by modulating specific kinase enzymes that serve as "hubs" for insulin-signaling processes.

More than 200 natural substances and extracts were tested for their influence on insulin responses and adipocyte (fat-storing) cells at the MetaProteomics Nutrigenomics Research Center. A combination of reduced iso-alpha acids (RIAA) derived from hops (*Humulus lupulus*) and acacia extract (*Acacia nilotica*) was shown via *in vitro* testing to inhibit inflammatory markers that influence insulin function.60

Research has implicated dysregulated inflammatory processes in the development of insulin resistance, and several inflammation-induced cytokines have been shown to be expressed during insulin resistance and metabolic syndrome.61-63 Cytokines—such as interleukin-1 beta (IL-1β), tumor necrosis factor alpha (TNF-α), and interferon gamma (IFN-γ)—have been shown to play a role in cytokine-induced β-cell dysfunction in diabetes.64,65

In human clinical testing at the Functional Medicine Research Center, supplementation of metabolic syndrome subjects with a combination of RIAA and acacia led to greater reduction of 2 h pp insulin levels, as compared to placebo. Furthermore, greater decreases of fasting insulin, fasting and 2 h pp glucose, fasting triglyceride, and HOMA scores were observed in subjects taking RIAA/acacia supplement versus subjects taking placebo. These collective results indicate RIAA/acacia supplementation might be useful in maintaining insulin homeostasis in subjects with metabolic syndrome.60
**Insulin SKRM Research**

![Graph showing increased insulin sensitivity with SKRMs](image)

*Figure 5. The Homeostasis Model Assessment (HOMA) estimates steady state beta cell function and insulin sensitivity, and is a published measure of insulin resistance. A significant decrease was observed for the RIAA/acacia group as compared to the placebo group in an 8-week clinical trial.*

![Graph showing improvement in triglycerides with SKRMs](image)

*Figure 6. In the same blinded, placebo-controlled study of 91 patients, the RIAA/acacia blend showed a greater improvement in triglyceride levels than placebo.*
Inflammation & Autoimmune SKRMs

Chronic inflammation, nutritional deficiencies, and oxidative stress are believed to be involved in the pathogenesis of autoimmune disorders. Mounting scientific evidence indicates that inflammation is also intrinsic to autoimmune conditions. In fact, during inflammation, an array of cytokines, eicosanoids, reactive oxygen species, and other mediators that can overwhelm and disrupt Th1/Th2 balance are released, which can potentially damage body tissues.66-69

People with chronic inflammation often have excess proinflammatory mediators. The present direction of research is the development of therapeutic agents that modulate the immune system by targeting specific cell types involved in the inflammatory response.

SKRMs in the form of reduced iso-alpha acids derived from hops (\textit{Humulus lupulus}) have been extensively tested for safety and effectiveness and professionally recommended as a safer option for joint relief for over 5 years—offering a high level of predicted cardiovascular, gastric, renal, and liver safety.70-78

RIAA still offers an excellent SKRM approach to inflammatory and autoimmune conditions. Recent nutrigenomics research, however, has identified even more powerful SKRMs from hops. Like RIAA, these new constituents, tetrahydro-iso-alpha acids (THIAA), offer a safer approach to modulating the arachidonic acid cascade. THIAA have also been extensively researched and tested—demonstrating the ability to modulate specific kinases associated with activities underlying joint tissue health and immune function, such as PGE$_2$ and TNF-$\alpha$.

THIAA have been shown in scientific testing to provide even greater targeted support with lower clinically effective dosing. In fact, in studies at MetaProteomics, THIAA have been shown to modulate induced PGE$_2$ production with two times greater effectiveness than RIAA, and to modulate induced TNF-$\alpha$ production with three times greater effectiveness.

Additional Support for Autoimmune Conditions

Common nutritional deficiencies associated with abnormal autoimmune response include inadequate vitamin D intake.79-81 The role of selenium and zinc has also been the source of heightened interest because of the role these nutrients play in metabolic processes involving joint tissues and immune system function.82-86
Figure 7. Cells were pre-incubated with THIAA or RIAA, followed by lipopolysaccharide (LPS)-induced stimulation of PGE₂ production. The data show that compared to the control and RIAA, THIAA inhibits PGE₂ expression more effectively.

Figure 8. Cells were pre-incubated with THIAA and then stimulated with LPS to induce TNF-α production. Results show that THIAA can lead to greater inhibition of TNF-α expression in a dose-dependent manner.
Future SKRMs

Nutrigenomic research continues to focus on naturally derived substances that act as SKRMs to beneficially influence health in other areas, such as liver detoxification, bone resorption, and hormone balance.

For more information on nutrigenomic research and the development of innovative nutritional protocols, please visit:
www.metaproteomicslabs.com
Phase 3
Recommending Key Nutritional Support

The following nutrients may provide complementary support for certain patients and offer a flexible and highly customizable nutrigenomic approach to wellness.

Cardiovascular Support

Coenzyme Q₁₀ (CoQ₁₀ or ubiquinone) and essential fatty acids (omega-3s) are both important for cardiovascular health. In addition to complementing nutrigenomic therapies, they may also play key roles in conventional therapies for CVD.

- **CoQ₁₀**—CoQ₁₀ plays an important role in the body’s energy-producing process. The body’s endogenous production of CoQ₁₀ decreases with age and dietary availability and absorption of CoQ₁₀ is rather limited, prompting the need for supplementation to correct a deficiency.⁸⁷⁻⁹⁹ CoQ₁₀ deficiency has been observed in patients with a variety of cardiovascular conditions—and patients with more advanced stages of CVD have been shown to possess lower levels of CoQ₁₀ than patients with milder forms of CVD.⁹₀⁻⁹³

  CoQ₁₀ levels can be further impacted by drugs in conventional therapies, such as statins that block its synthesis.⁹⁴⁻⁹⁶ Fortunately, statin-induced CoQ₁₀ deficiency can be prevented with supplemental CoQ₁₀ with no adverse impact on the cholesterol-lowering or anti-inflammatory properties of statin drugs.⁹⁶,⁹⁷ Scientific studies have also shown that CoQ₁₀ may be recommended as preventive therapy or as a safe and effective adjunct to conventional therapy for CVD.⁹⁷⁻¹₀₂

- **Essential Fatty Acids (EFAs)**—Omega-3 fatty acids, such as those found naturally in cold-water fish (including EPA and DHA), have been examined in previous clinical and epidemiological research that has shown they may.⁹⁸⁻¹⁰⁵

  - Decrease the risk of fatal arrhythmias
  - Decrease triglyceride levels
  - Decrease growth rate of atherosclerotic plaque
  - Lower blood pressure (slightly)
  - Decrease the chance of stroke

  *Note: Clinical tests have also shown that people with diets rich in EPA are less prone to inflammation in joints, intestines, lungs, and skin.*
Blood Sugar Metabolism Support

Ever-growing research continues to show the newly discovered benefits of green tea and cinnamon in complementing dietary approaches to blood sugar management. Insulin resistance conditions can also induce oxidative stress that can lead to vascular complications, such as neuropathy.

- **Cinnamon**—Cinnamon has been shown to display insulin-enhancing activity in vitro and shown in human clinical trials to positively influence glucose levels.\(^{106-108}\) Extracts of cinnamon have also been shown to activate insulin receptor kinase and inhibit dephosphorylation of the insulin receptor—leading to increased insulin sensitivity.

- **Green Tea (EGCG)**—Green tea contains epigallocatechin gallate (EGCG), a bioflavonoid shown to protect pancreatic islet cells and enhance insulin sensitivity.\(^{109}\) Catechins from green tea also provide strong antioxidant protection.\(^{110}\)

Liver Detoxification Support

There are two primary phases in the detoxification process. In Phase I, fat-soluble toxins are transformed into intermediate compounds that are more reactive, but will bind more easily to non-toxic, water-soluble molecules in Phase II. In Phase II, formation between the reactive intermediates and water-soluble molecules make the entire compound ready for excretion out of the body. Targeted nutrients can influence detoxification activities in either phase—or sometimes both.

- **Silymarin**—This active constituent of milk thistle (Silybum marianum) is well-recognized for its beneficial effects on protecting the liver from toxins and stimulating liver regeneration, as well as its antioxidant properties. Preliminary research also indicates that it may influence Phase I and Phase II enzymes, and therefore may be called a bifunctional modulator.\(^{111,112}\)

- **Catechins**—These strong antioxidants have the capacity to scavenge most oxygen free radicals.\(^{110}\) Also derived from green tea (Camilla sinensis, see above), catechins enhance the induction of Phase II enzymes—glutathione S-transferase and quinine reductase—and inhibit the overinduction of specific cytochrome P450 Phase I biotransformation enzymes.\(^{113,114}\)

- **Watercress**—Glucosinolates found in watercress (Nasturtium officinale) are precursors of phenyl isothiocynate (PEITC), which effectively inhibits the overinduction of specific cytochrome P450
enzymes and enhances Phase II glutathione S-transferase and quinine reductase.115-117

- **Ellagic Acid**—Naturally found in pomegranate fruit (*Punica granatum*), ellagic acid beneficially modulates Phase I biotransformation and enhances Phase II glutathione S-transferase and quinine reductase enzyme induction.118-120 Also scavenges superoxide radicals and hydroxyl radicals, reducing hepatic oxidative stress.120,121

  *Note: Catechins, watercress, and ellagic acid also influence genetic expression of enzymes that control Phase II conjugation reactions.*113-120

- **Artichoke Leaf**—Extracts from artichoke (*Cynara scolymus*) have a long history of traditional use in promoting liver function. Research suggests that several constituents of artichoke, including chlorogenic acid and cynarin, have marked antioxidant and hepatoprotective properties.122-124

**Intestinal Support**

Probiotic strains have specific characteristics that determine whether they have the ability to benefit the intestinal environment. But not all genera, species, and strains are suitable for all purposes. Following are beneficial bacteria shown to adhere to the intestinal lining and support a healthy balance of microflora.125-130

- **Lactobacillus acidophilus NCFM®**—This strain of human origin has been proven safe and effective by more than 60 scientific studies and almost 30 years of commercial use. It produces lactic acid, hydrogen peroxide, and other natural substances while modulating the activity of enzymes—such as β-glucuronidase, nitroreductase, and azoreductase—to positively influence the balance of intestinal bacteria and support intestinal tissue health.125 It’s also one of a limited number of *Lactobacillus* species shown to adhere in the intestines.131

- **Bifidobacterium**—This major group of carbohydrate-metabolizing bacteria in the intestines (including *B. lactis*) is 1000 times more abundant than lactobacilli in healthy adults (and some researchers believe more important as well).132 Bifidobacteria have proven effectiveness as immunosupportive agents that enhance host resistance, as well as produce strong acids (e.g., acetic, lactic) that positively affect intestinal pH; thereby, playing a critical role in modulating ammonia, phenol, steroidal, and other toxin levels to maintain health and support intestinal microbial balance.125-127
Note: Scientific identification of strains is not only an indicator of predicted safety, but assures the means for providing optimal health benefits.

**Joint Inflammation Support**

Many inflammatory and autoimmune conditions are characterized by pain and motility concerns related to the joints. Glucosamine and chondroitin sulfates, as well as MSM, offer widely accepted approaches for maintaining healthy connective tissue and relieving pain associated with concerns that affect a growing number of patients.

- **Glucosamine & Chondroitin**—These nutrients are naturally found in healthy tissue and work together in forming healthy joint matrix cartilage and enhancing joint lubrication. They may also promote the incorporation of sulfur into cartilage. Sulfur is necessary for the synthesis of collagen and improves the moisture content of cartilage, supporting its shock-absorbing ability. Supplementation with glucosamine and chondroitin can help restore normal joint motility and relieve pain. Continued use is required to maintain benefits.

- **Methyl-Sulfonyl-Methane (MSM)**—This natural compound complements glucosamine and chondroitin sulfates, and also provides a highly biologically valuable source of sulfur. MSM has been widely used to support joint health and relieve pain as an effective natural analgesic and anti-inflammatory agent. A randomized, placebo-controlled trial showed that MSM improved symptoms of pain and physical function in patients with osteoarthritis. Another randomized, double-blind, parallel, placebo-controlled trial also showed that MSM significantly improved the signs and symptoms of osteoarthritis. Furthermore, the combination of glucosamine and MSM showed better efficacy in reducing pain and swelling and in improving the functional ability of joints than the individual agents.

**Hormone Balance Support**

Phytoestrogens are plant compounds that have structural and functional similarities to estrogen. Selective estrogen receptor modulators (SERMs—not to be confused with SKRMs) are non-steroidal compounds capable of binding to the estrogen receptors and influencing their activities. Specifically, SERMs are noted as being both agonists (in cases of low estrogen levels, such as with menopause) and antagonists (in cases of high estrogen). Because they support a moderate level of estrogen activity, upon binding to the estrogen receptors they inhibit endogenous estrogen when too much is present, but can still support estrogen’s important functions.
• **Kudzu & Red Clover**—Provide a varied profile of non-soy isoflavones and isoflavone glycosides—including daidzein, genistein, puerarin, and fromononetin—that bind to the estrogen receptor and may act as weaker estrogens, resulting in an inhibition of the estrogenic effect.\(^{50,144-146}\)

• **Turmeric**—Curcuminoids, the active component in turmeric (*Curcuma longa*), induce glutathione production and glutathione-S transferase activity—helping to protect tissues from reactive estrogen metabolites.\(^{147}\) In combination with isoflavones, curcumin shows *in vitro* evidence of reducing xenoestrogens-induced growth in estrogen receptor-positive and –negative cancer cells, thereby promoting breast health.\(^{55,148}\)

• **Resveratrol** (from *Polygonum cuspidatum*)—Classified as a SERM based on its ability to bond to estrogen receptors and act as both an estrogen agonist and antagonist. Resveratrol provides many other benefits, including cardioprotective properties.\(^{149}\) Resveratrol has been shown to promote healthy cytokine production by influencing the cyclooxygenase and 5-lipoxygenase pathways. It is also associated with reduced activity of nuclear factor kappaB (NF-κB)—a transcription factor that may promote the expression of undesirable genes. Resveratrol has potent antioxidant activity (especially in lipids that are highly concentrated in brain tissue), promotes healthy blood flow, and induces hepatic phase II detoxification activity.

• **Stabilized Indole-3-Carbinole (I3C)**—This naturally occurring compound found in cruciferous vegetables protects estrogen-sensitive tissues by promoting the formation of 2-hydroxyestrone, diindolylmethane (DIM), and other beneficial estrogen metabolites. It supports the detoxification of estrogens, other steroid hormones, and xenoestrogens by enhancing the activity of enzymes involved in their metabolism and excretion. Research indicates great promise as a natural hormone-balancing agent.\(^{150-157}\)

*Note: Natural-source I3C may be an important consideration when recommending supplementation to patients.*
Putting It All Together

The Nutrigenomics Matrix (provided on page 3) gives you a top-line overview of implementing nutrigenomics in your practice for a broad range of patients. Determine the appropriate level of support for your patients, as well as the components that complement the structure of your practice.

For further assistance, the FirstLine Therapy program also provides diagnostic tools and assistance in determining appropriate nutritional support based on symptoms and in-office measurements. It also provides helpful materials for educating and motivating patients, as well as monitoring their progress.

As always, the Metagenics Technical Support team of professionals is available to answer questions regarding products and clinically tested nutritional protocols.

About Metagenics, Inc.

Metagenics is a life sciences company and leading developer and manufacturer of professional grade, science-based medical foods and nutraceuticals sold to healthcare practitioners worldwide. For more than 25 years, Metagenics has been a leader in quality, scientific discovery, and innovation, with multiple proprietary formula patents and more than 400 research-based products to optimize health. The company is headquartered in San Clemente, CA, with manufacturing and research facilities located in Gig Harbor, WA, including the MetaProteomics® Nutrigenomics Research Center and the Functional Medicine Research CenterSM for human clinical research. For more information, please visit www.metagenics.com.

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APPENDIX A

Applying Nutrigenomics for Children & Teens

A nutrigenomic approach to wellness doesn’t have to wait until adulthood. With the rise of metabolic syndrome and other conditions in children and teenagers, your younger patients may already be in need of some beneficial signal modification. And you can help them now.

The following medical food programs offer targeted nutritional support and complementary dietary programs to address the nutritional management needs of children and teens. Customize these programs with other nutrients to address specific needs.

Metabolic Syndrome

_Ultracare First Start™ Medical Food_ is formulated to provide specialized nutritional support for children and adolescents ages 6-18 with metabolic syndrome, obesity, dyslipidemia, and insulin resistance by supplying a low-glycemic-index blend of macro- and micronutrients, including cinnamon, chromium, and heart-healthy soy protein and isoflavones. This unique formula:

- Addresses the protein needs of growing children and teenagers by providing 6-12 grams of soy protein per serving.
- Supplies cinnamon to help maintain healthy glucose and insulin function.
- Provides a good source of dairy-free calcium and magnesium to support peak bone mass development.

Atopic Disorders

_Ultracare for Kids® Medical Food_ is formulated to provide specialized nutritional support for children with food allergy-related symptoms and atopic disorders by supplying readily assimilable, low-allergenic-potential rice protein.

- Low-allergenic-potential rice protein to complement restricted diets.
- The rice protein has been prepared via a unique process that reduces the already low-allergenic potential of rice protein.
- Provides fructooligosaccharides (FOS) to promote the growth of bifidobacteria, which may help encourage healthy, balanced immune function in young children.
- Supplies dairy-free calcium to support bone health and new bone formation.
- Provides high quality foundation nutrition for children up to 12 years of age.

Comprehensive dietary recommendations and other lifestyle guidelines are available for parents to help implement and monitor.
APPENDIX B

The Need for Therapeutic Lifestyle Changes

A white paper discussion on the scientific basis for and effectiveness of therapeutic lifestyle changes (TLC) programs has been prepared for your reference. This paper is entitled “The Chronic Disease Epidemic: A Prescription of Primary Prevention and Profitability” and is available upon request at: www.metagenics.com/flt/whitepaper_request.asp

Also included are practical tips for evaluating a TLC program to fit the needs of your practice.

Further information for patients and practitioners on the FirstLine Therapy TLC program is also available at www.metagenics.com.

