metabolite level, such as nutrient signaling, energy production, cell repair, and immune health. These metabolites are a much more accurate way of assessing cell health compared to genes, because it closely reflects what is happening within the cell at that exact time.[1,3,5] It directly reflects everything your body is currently experiencing including changes to diet and nutrition, inflammation, toxin exposure, and lifestyle changes.[8]

Along the pathway of gene expression and metabolism, there are places where the road is rocky. By identifying predispositions to bumps in the road and making recommendations on how to modify both epigenetic expression and metabolism, practitioners have a road map to keep each patient on smooth pavement. Large clinical studies are leading the way for personalized nutrition by exposing the variance that occur between people and developing testing methods sensitive enough to detect these changes so that dietary and lifestyle recommendations can be precisely targeted.[9,10] Immune response, Inflammation, methylation, energy production, hormonal health, GI health and detoxification continue to emerge as the cornerstones of health and wellness.[6,11,12] These cornerstones are all founded in how patients express their genes and metabolize the products. Currently, nutritional recommendations are set for a wide population and to address the nutrition of the average human. However, we are aware that large variances occur from person to person and the one-size-fits-all approach is far from suitable for patients seeking epigenetic and metabolic optimization. This strategy thereby avoids having patients over or under consume specific nutrients in a quantifiable manner aiming for high metabolic performance and preventative health.

Recent advances in the omics field

In the past, analytical limitations made life relatively simple, and the nutritional biochemist dealt with perhaps a half-dozen metabolites, developed an integrated theory

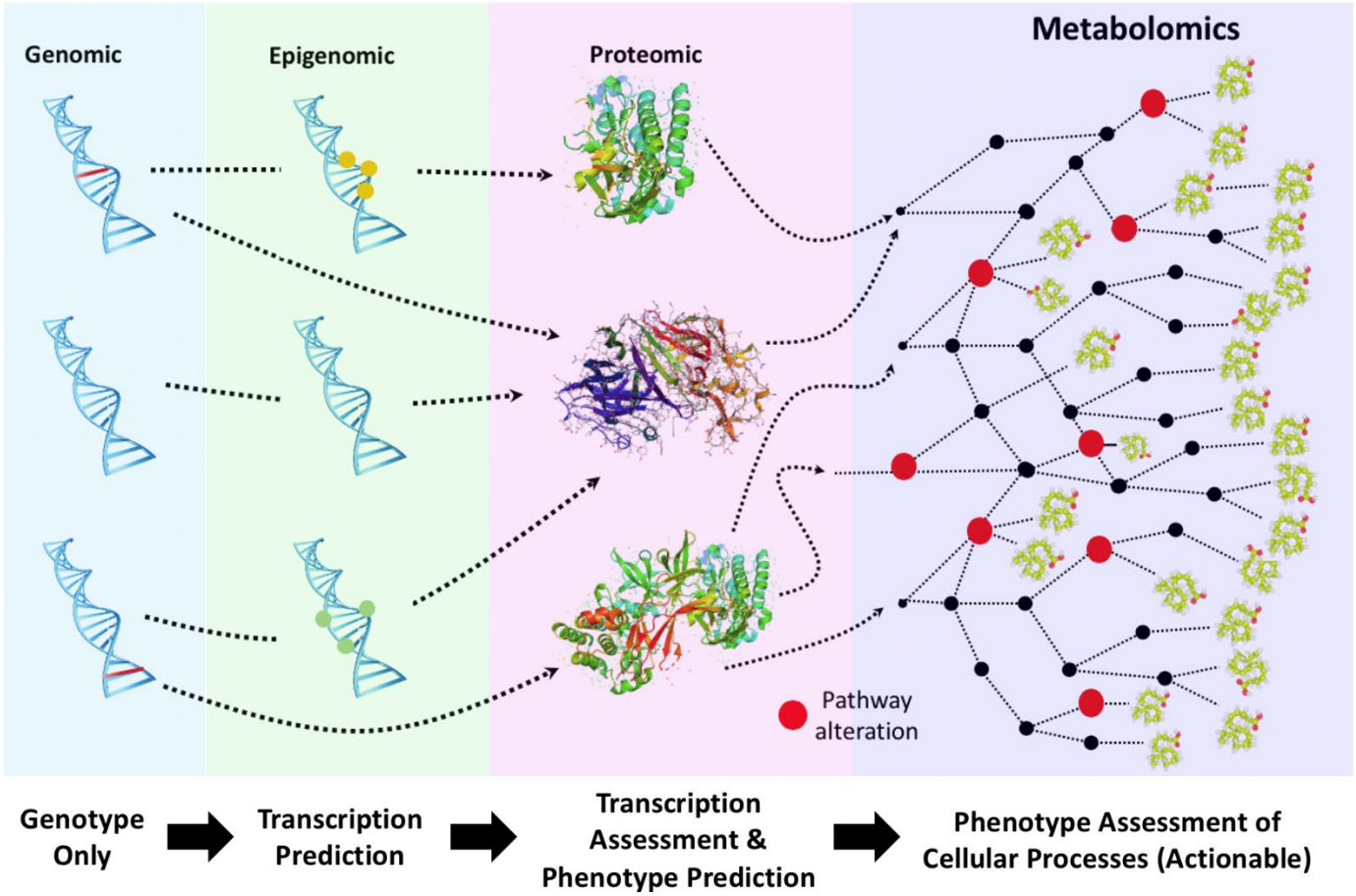

Figure 2. A schematic of the -omics indicating how greater phenotypical information is gained from left to right.

for how they related to each other, and predicted the effects on cell function or disease. Nowadays with the advent of new technologies and smart software, scientists have the ability to simultaneously assess thousands of metabolites.[13,14] This greatly improves the ability to resolve even the most subtle metabolic differences that exist between individuals and provide information on how to address imbalances, deficiencies and disease. High-throughput genotyping methods gave rise to large-scale Genome-Wide Association Studies (GWAS) over a decade ago, with the promise to elucidate the genetic basis of complex diseases. Many traits have since been correlated with single nucleotide polymorphisms (SNPs), including metabolomics measurements from human cohorts.[9,15] This provides a detailed *in-vivo* picture of the influence of genetic variation on the real world-implications. Not only are these systems allowing for diagnostics of disease, they offer the ability to closely monitor metabolic performance to maintain optimal nutrition, proactively prevent disease and improve overall quality of life.

The relationship between genes, metabolism and nutrition

The concept of epigenetic nutrition looks at how diet, supplements, lifestyle and environment contribute to altering gene expression through methylation and modification. Epigenetic gene modification is very different from person to person, and dependent on the molecular machinery involved in gene expression resulting in the individuals' phenotype. As such, the nutrient requirements are also dependent on these mechanisms. Through epigenetic biomarker analysis, one can take advantage of knowing which parts of the molecular machinery are not functioning correctly and rectify it by implementing metabolic correction through personalized nutrition, lifestyle and environmental changes. These epigenetic changes can result in modifications that affect metabolism in humans.[16] Relations between diet, epigenomic and metabolomic profiles and between those profiles and health have become important components of research that have revolutionized clinical practice in nutrition and preventative health.[14] We know that metabolic alterations produced by excessive intake of some nutrients, drugs and chemicals directly impact epigenetic regulation and corelate how metabolic pathways are modified by environmental and genetic factors, providing novel insights for the treatment of metabolic imbalance and diseases. For example, elevations in the levels of 6 amino acids predicts a significantly high risk of diabetes up to 10 years in advance.[1,17,18] Integration of multi-omic assessments are allowing scientists to link together all the different systems involved in human metabolism and quickly making connections to nutrient absorption, elimination and physiological function.

There are 3 major conceptual groupings for thinking about nutrient-gene-metabolism interactions: i. direct interactions: nutrients, sometimes after interacting with a receptor, behave as transcription factors that can bind to DNA and acutely induce gene expression; ii. epigenetic interactions: nutrients can alter the structure of DNA (or of histone proteins in chromatin) so that gene expression is chronically altered; and iii. common genetic variations, SNPs, can alter the expression or functionality of genes.[1,5] All of these mechanisms can result in altered metabolism of and altered dietary requirements for nutrients. Diet and nutrition play a role in epigenetic modification by causing by sustained effects of gene expression, mainly by a process called methylation.[19] When methylation occurs in gene promoter regions, expression is altered. Increased methylation usually results in gene expression reduction or silencing. Epigenetic modifications can result in changes in gene expression that can last throughout a person's life and can even persist across generations.

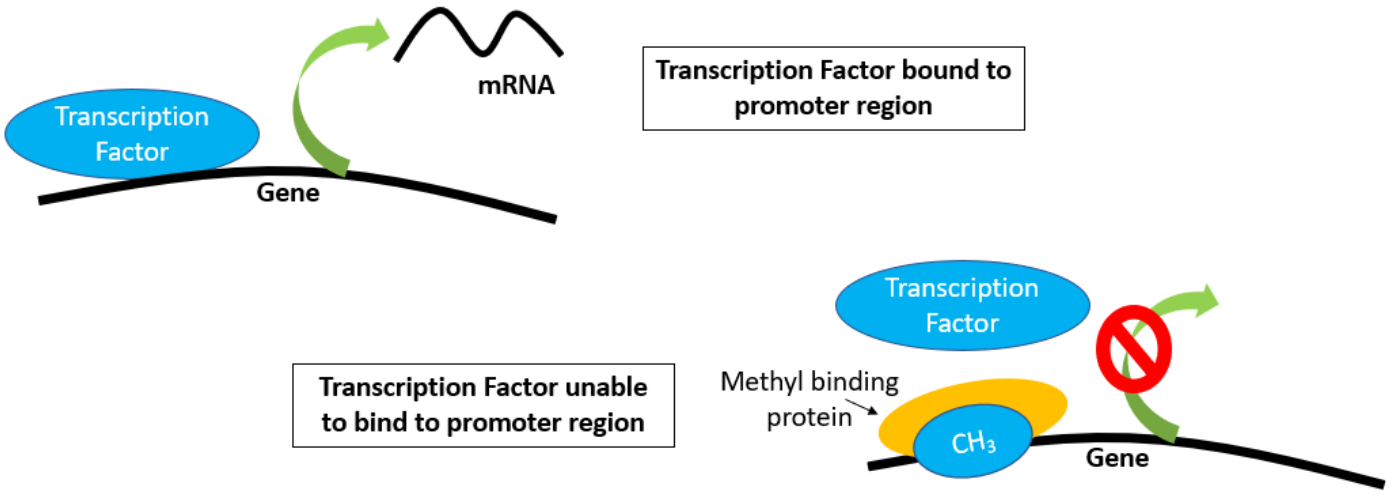

Figure 2. DNA methylation can silence gene expression. Methylation of cytosine located in cytosine-guanosine groupings in gene promoter regions (called 5'-CpG-3' islands) attracts capping proteins that hinder access to the gene for the transcription factors that normally turn on gene expression and formation of messenger RNA (mRNA). When the transcription factor does not bind to the promoter area of the gene, transcription of mRNA does not occur, and the gene is silenced.

It has been shown that nutritional factors have a major influence on gene expression and metabolism. Changes to mRNA and expression profiling and the corresponding proteins regulate the transport of certain nutrients and metabolites. As a result, a clinically actionable approach can focus upon nutrition and other modifiable lifestyle factors to achieve optimal gene expression, and therefore improved optimal health. Due to metabolic individuality, sub-groups of a population may respond differently to dietary intervention. An example of this is the use of folic acid in a population lacking the methylene tetrahydrofolate reductase (MTHFR) gene, this population would need the activated form of folic acid in order to benefit from this supplement, since they cannot convert it naturally.[20,21] Further, genetotrophic disease occurs from suboptimal consumption of nutrients necessary to meet the epigenetically determined requirements of the individual. Quantitatively identifying these deficiencies and supplementing them through personalized nutrition affords optimal metabolic performance and disease prevention. Examples of physiologically critical nutrients include micronutrients such as vitamins and minerals, which exist to enhance enzyme efficiency. Vitamins are co-factors for enzymes, and enzymes are proteins that may be altered due to epigenetic changes thereby affecting their intended function. In order to have enzymes functioning at their maximal capacity sufficient active cofactors must be present, and deficiencies can be addressed through specific nutritional interventions. Maintaining the correct balance of nutrients will ensure that the complex epigenetic molecular machinery of the body is running at optimal efficiency via metabolic correction.

Amongst all the *omics,* metabolomics plays a special role. The metabolome is the set of all small molecules, such as amino acids, sugars and lipids, in a biological system. It is considered to be an endpoint of biological processes and carries an imprint of all genetic, epigenetic and environmental factors.[2,3,14] It has therefore also been referred to as the 'link between genotype and phenotype'.[4] Epigenetics is linked to metabolomics in response to the cellular microenvironment. The metabolism of various biochemicals such

as amino acids, organic acids and fatty acids are critical in this linkage between epigenetics and metabolism. As such, metabolomics is a direct representation of the outcome of epigenetic modifications in the human body – it quantifies the metabolic response of pathways dependent on epigenetics; diet and environmental factors. Genomics and proteomics provide you with information about what might happen, whereas metabolomics provides you with information about what is happening. Individual metabolites have already been used as epigenetic biomarkers for years. Elevated estrogen, for instance, is indicative of a genetic modification affecting the aromatase enzyme which is responsible for conversion of testosterone to estrogen.[22,23] Another example, 8-OH-dG, is a metabolite produced from DNA damage and oxidative stress.[24–26] Metabolomics enables the identification of such biomarkers based on epigenetic and environmental disruptions to the biochemical pathways that are up/down-regulated in unison. Assessing epigenetic dependent metabolites provides in-depth and actionable information allowing for personalized treatment and nutrition strategies to address imbalances and restore optimal cellular health. Since the metabolic profile of a patient is a consequence of many contributing biological systems, the dynamic balance of the body's biochemical pathways can be mapped out with high precision and a fundamental understanding of their specific roles in being healthy.[6,27] Further, metabolomics affords rich data by repeated sampling that clearly shows how all the different metabolites can change, and be measured.

Just as the published Human Genome Project is an average representation of genes in humans, there is the Human Metabolome Data Base (HMDB) which is an accurate representation of every metabolic pathway possible for humans.[10,28] However, there is significant variation from the average in both genome and metabolome in any given individual. Metabolomics can identify mechanisms that underlie individual variations in dietary requirements as well as in the capacity to respond to food-based interventions in a spatial and time-dependent manner more than any other *omic* alone. Each metabolite can be traced back to specific function thereby allowing for clinically actionable, outcome-based solutions to promote metabolic balance. Doctors, clinicians and nutritionists are rapidly harnessing the power of metabolomics with great success in treating many of the chronic disease responsible for 88% of deaths per year.[26] Metabolomics has the potential to transform the health of entire populations through integrative and preventative health strategies by guiding diet, supplementation and lifestyle changes. Nutrition is one of the best ways to prevent a variety of diseases and health issues in the body.[4,30] Optimizing nutrition is done by identifying subtle imbalances, deficiencies and metabolic issues. It can help a practitioner target specific nutritional requirements to alleviate current symptoms and lower risks of certain diseases in the future.[6] A balanced, personalized diet will ensure a person is receiving the correct amount of nutrients such as vitamins and minerals, amino acids, fatty acids and much more. This all works to keep the body running at maximum efficiency with more energy, improved metabolism, stable weight, less inflammation and a healthy heart and brain.

Using the omics to tailor personalized nutrition

Epigenetic dependent metabolism involves a vast array of chemical reactions; of particular importance are those involved in the transfer of functional groups. When a methyl group, for example, is added to a particular molecule, it may change its activity. This simple chemical reaction allows cells to use metabolic intermediates to carry chemical groups between different reactions. These group transfer intermediates are called cofactors or coenzymes. Each transfer reaction is facilitated by a particular coenzyme. These coenzymes are continuously being made, consumed and then recycled. Nutrition has a sequential effect on the epigenome and metabolome which can produce either a healthy physiological state or fundamental metabolic disruption such as excessive inflammation, oxidation, neurological and metabolic stress.[31] Dietary constituents have been shown to alter gene expression in a

Gene	MPP Biomarkers	Mechanism of Action	Physiological Complications	Nutritional Interventions
MTHFR C677T	Homocysteine	(T,T) homozygous for C677T of MTHFR = 10-20% efficiency in processing folic acid = high homocysteine, low B12 and folate levels. Billions of times per second, the body repairs DNA during the process of methylation. Additionally, methylation is crucial in the detoxification and elimination processes of many biochemical pathways and cycles in the human body and help maintain homocysteine balance for optimal cardiovascular health, proper neurotransmitter production and healthy energy metabolism.	If vitamin-dependent biochemical processes are stalled due to an lack of folate and other methylation cofactors, breakage of DNA strands and metabolism alterations can occur. Increases in homocystine are associated with osteoporosis and central nervous system disorders and increased risk of atherosclerosis, cardiovascular disease, ocular, muscular, neurological and joint complications.	These pathways can be restored to homeostasis through the nutritional support of Folate, Trimethyl Glycine, and B-vitamins. Elevated homocysteine with normal methylmalonic acid, B6 or Folate is recommended. Homocystine is inversely correlated with Folate, and B12 in blood so as these are increased (through supplementation), homocysteine levels decrease accordingly.
MTR	Methionine and Homocysteine	Polymorphisms in this gene lead to poor recycling of methionine from homocysteine. Homozygous for this gene results in low methionine and high homocysteine levels.	Methionine is important due to its ability to methylate proteins and DNA. Increased methionine can also be an indication of GI bacterial overgrowth. Low levels can indicate impaired liver function and can be corrected through a balanced amino acids replacement. Low Methionine is usually caused by poor diet that is generally low in amino acids.	Low levels can cause low cystine, taurine and glutathione without proper supplementation to either replace methionine or downstream cofactors. Recommend amino acid replacements therapy.
MTRR A66G	Methionine	Methionine Synthase Reductase is a enzyme responsible for production of methionine, a very important amino acid.	Increases the risk for: metabolic syndrome, congenital heart disease and male infertility.	The three bioavailable forms of B12: Methylcobalamin, hydroxycobalamin, and adenosylcobalamin. Polymorphisms in methionine are fairly common and require an increased amount of Methyl B12, Folate and Zinc to help this reaction.
TCN1	Methylmalonic acid	This gene mutation results in low Vitamin B12. Methylmalonic acid is a Vitamin B12 biomarker.	Increases the risk for: metabolic syndrome, congenital heart disease and male infertility.	Vitamin B12, when tHCys is also elevated, B6, B12, Folic Acid and methyl donors.
TCN2	Methylmalonic acid and homocysteine	Individuals with the G/G phenotype at rs1801198 have decreased serum B12 and increased homocysteine when compared to individuals with the C/C phenotype. Methylmalonic Acid (MMA) is converted to succinic acid in the presence of Vitamin B12 as well as methionine from homocysteine leading to an increase in both MMA and tHCYS.	Some increase in peripheral neuropathy risk in older adults taking folate. Issues with energy production, methylation and detoxification.	Vitamin B12, when tHCys is also elevated, B6, B12, Folic Acid and methyl donors.
ATP5C1	Carnitine and Ornithine	ATP5C1 is an enzyme responsible for producing ATP (the energy component) in the mitochondria. L-Carnitine is required to shuttle fatty acids across the mitochondrial membrane for use in oxidation and energy production. Ornithine is an essential cofactor to energy production. Optimal mitochondrial biogenesis, is critical for the promotion of healthy aging, optimal energy production, and protection from reactive oxygen species (oxidative stress).	Elevations in ornithine and carnitine can indicate hyperammonemia, deficiencies in Vitamin B6, magnesium and alpha-ketoglucaric acid, bacterial overgrowth of the gut and taking too much L-Lysine supplementation. Low levels caused by excessive ammonia, fibromyalgia, protein deficiency and malnutrition.	Elevated recommendations: Vitamin B6, magnesium and alpha-ketoglucaric acid. Low recommendations: amino acid replacement therapy.
IDO1	Tryptophan and Kynurenic Acid	IOD1 codes for an enzyme that catalyzes the first and rate-limiting step in tryptophan catabolism to N-formyl-kynurenine. This enzyme is thought to play a role in variety of pathophysiological processes such as neuropathology and immunoregulation. Buildup of tryptophan can cause apoptosis of T cells and a decrease in T regulatory cell numbers. Increased levels are also associated with oxidative stress, diabetes and shifts in brain physiology that can lead to neurological disorders.	Increased kynuric acid correlates with increased levels of its precursor xanthurate. Increased kynuric acid is an indication of B6 deficiency and is also an indication of oxidative stress risk. Elevated levels of tryptophan are usually associated with dietary excess but can be associated with a rare genetic disease (Hartnup disease). Low tryptophan is associated with disorders such as insomnia, depression, anxiety, bipolar disorder and migraines.	Anti-Inflammatory Therapy: Curcumin, Omega 3s, Resveratrol, Quercetin, prescription low dose Naltrexone (LDN) and CBD Oil. Vitamin B6 for elevated kynurenic acid. Elevated tryptophan will benefit from Niacin, B6, iron, copper. Low tryptophan will beenfit from 5-HTP and amino acid replacement therapy.
ATG12	8-OH-dG	Mutations in the ATG12 gene are predicted to lead to increased activity of the innate immune response, and overall inflammation. ATG5 is involved in a wide range of "quality control" features inside the cell: autophagy vesicle formation, innate immune system signaling, consumption of damaged mitochondria, and apoptosis. Mutations in the ATG5 gene are associated with numerous neurological, immunological and endocrine syndromes. 8-OH-dG is indicative of oxidative stress or cofactors and recovery mechanisms required to maintain the normal flow of mitochondrial respiration (the greatest source of ROS).	Oxidative stress is a condition that results in increasing levels of free radicals that create an environment of increasing cellular damage over normal cellular function. While cellular damage and is always present, antioxidants act as scavengers of reactive oxygen species (ROS) and free-radicals to maintain a balance between cellular function and cellular damage. Additionally, certain gut dysbiosis and other inflammatory actions contribute to this. Patients may have increased risk of Type 2 Diabetes.	Therapies should include Curcumin, Sulforaphane, Ginseng, Lithium Orotate, D- Chiro-Inositol, Catechins and Resveratrol. Antioxidants (Vitamins A, E, C, beta-carotine, CoQ10, lipoic acid). Routine exercise and 12-15 Hour Fasting is should be added to daily lifestyle.
AOC1	Histamine	When polymorphisms are present, the ability to break down external histamine will be poor. Under healthy conditions, the gastrointestinal (GI) tract contains a semipermeable epithelial mucosal barrier which protects against the unwanted passage of food antigens, toxins, and microorganisms from crossing directly into the bloodstream. Several factors can affect the integrity of the epithelial barrier including medications (particularly NSAIDs) non-steroidal anti-inflammatory drugs), stress, alcohol intake, injury, trauma, microbial imbalance and poor nutrition.	Significant increases can be seen in people with a severe allergic reaction and in those with a disorder in which the number of mast cells increase (proliferate) and/or activate without apparent allergies. Histamine is cleared in a copper-dependent step so elevated levels may indicate a need for copper. The brain can utilize excess histidine to produce histamine and chronically elevated histamine may appear as low histidine levels because of this conversion. Reducing the impact of these factors and preserving a healthy GI tract is critical for maintaining long term health.	May have difficulty with foods containing histamine. Elevated histamine casues llergic reactions, inflammation and certain disease states associated with mast cell proliferation. Treat with copper and decrease exposure to irritants and allergens.
CBS C699T	Taurine	Those who are CBS C699T, CBS A360A, or CBS 212 may tend toward high taurine levels. This can cause problems with sulfur processing and potentially deplete B12 and molybdenum. High levels of taurine also can cause low levels of GSH.	Taurine is a conditionally essential amino acids that can be synthesized by cysteine when B6 levels are adequate. Elevated levels can indicate liver issues or muscle damage but are usually associated with high-taurine diets. Vegetarian diets may also have low levels of taurine and may require Taurine supplementation.	Elevated recommendations: Zinc, Antioxidants (Vitamins A, E, C, beta-carotene, CoQ10, lipoic acid). Low recommendations: B6, amino acid replacement therapy.

Table 1. Examples of Epigenetic and Nutritional Dependent Biomarkers.[17,32-43]

number of ways: i. Acting as ligands for transcription factor receptors; ii. by being metabolized in primary or secondary metabolic pathways thereby altering concentrations of substrates or intermediates; and iii. by altering signal transduction pathways.[27] Although epigenetics does not result in changes to the nucleotide sequence, it does comprise molecular modification of DNA and histones. Since information flows in both directions (i.e., from genetics to metabolites and vice versa), gene expression can also be activated or deactivated by signals from the environment.

Dietary factors, such as the daily intake of folate, can be considered as an environmental stimulus with the potential to affect gene activation through, for instance, a change in the DNA methylation status. Accordingly, genes alone do not determine biological fate; it is the response to environmental and nutritional stimuli that actually determine the gene expression.

Every human is completely unique and requires specific nutritional considerations for optimal health. These needs are dependent on a variety of factors including genetics, diet, lifestyle and environmental influences. Through complex software and analysis, scientists have been able to elucidate and map out the patterns and dynamic balance of metabolic pathways, eg: groupings of related genes that regulate metabolic pathways and then groupings of related metabolic pathways. In order to rectify epigenetic and metabolic issues, one must address the symptoms of nutritional, metabolic and detoxification issues. Providing personalized nutrition for individuals allows for an optimal diet, improved metabolic performance and disease prevention.[32] For this reason, most nutrition scientists immediately grasp the advantages gained from being able to measure many metabolites rather than a few. In the past, analytic limitations made life relatively simple, and the nutritional biochemist dealt with perhaps a half-dozen metabolites, developed an integrated theory for how they related to each other, and did an excellent job in predicting the effects on cell metabolism. Nowadays, advances in biotechnology instruments permit the analysis of thousands of metabolites simultaneously and massively increases diagnostic power and accuracy. Integrated platforms that combine the facets of genes, epigenetic modification and metabolism are essential to understanding their roles in the human body.[33,34]

The Epigenetic Biomarker Panel (EPB) from Physicians Lab is a simple and fast urinary metabolomics panel quantifying over 60 epigenetic and nutrient dependent metabolites using the gold standard of bio-analytical equipment, Liquid Chromatography with tandem Mass Spectrometry (LC-MS/MS). The results provide detailed information on how the body is metabolically and nutritionally balanced thereby allowing for highly specific, personalized therapeutic strategies. Metabolism is a complex process, and through the Metabolic Performance Profile, one can identify how nutrients are used to fuel critical biochemical reactions within the body. The Metabolic Performance Profile quantifies key categories which affords the determination of personalized nutrient and supplement recommendations. The results are driven by algorithms to determine outcome-based recommendations which are supported by peer-reviewed clinical literature and population wide association studies.

Most traditional nutritionists and dieticians believe that the requirements for minerals are met simply with a conventional balanced diet, however this may ignore biochemical individuality. The optimum intake of micronutrients for each person will vary according to age, genetic makeup, diseases, and exposure to stress and toxins. The failure to apply the concept of biochemical individuality may negatively impact an individual's efforts to reach metabolic optimization. Conversely, it has been proposed that a metabolic tune up could produce a marked increase in health in certain individuals. Every physiological component must be considered in order to perform at peak efficiency. Metabolic processes can be viewed as links in a chain. The strength of the entire chain can be compromised by only one weak link. However, a significant portion of the American population does not even reach the Recommended Daily Allowance (RDA) of some critical nutrients from their diet.[45] A state of subclinical deficiency or dietary insufficiency seems prevalent and may have serious health consequences. Supplementation with specific nutrients has been estimated to be cost effective in preventing diseases. Food alone may not provide sufficient micronutrients for preventing deficiency or insufficiency. Many older adults do not consume sufficient amounts of numerous necessary nutrients from foods alone. Supplements compensate, but only an estimated half of this population uses them daily, so having an easy daily solution is key to addressing the issue. Scientific formulations capable of

multifunctional synergy with the ability to support healthy epigenetics and metabolomics should be an area of focus. This approach can produce a partnership with healthcare professionals that will allow individuals to optimize their health regardless of their underlying genetics.

Future Prospects

There are a number of medical and economic implications to the development of nutritional epigenetics and metabolism optimization strategies: i. to prevent diseases is economical, since prevention is less expensive than treatment; ii. to lessen the cost of healthcare is imperative, since healthcare or better yet disease- care cost is too high and continues to increase; iii. to educate the public in this new health paradigm, so they can start taking better care of themselves; iv. to make science accessible, in all terms, especially economically; so that medication, supplementation and metabolic optimization costs can be lower.

It is apparent that a niche will exist for health professionals who can effectively place the new information generated by metabolomic profiling into a context that enables integration, interpretation, and, subsequently, individualized dietary recommendations. Thus, the field of nutrition would benefit by establishing itself as the predominant discipline using this knowledge in clinical and public health practice.

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