NRI
NEUROLOGICAL RESEARCH INSTITUTE

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Methylation Pathway Analysis
JOHN DOE

READ IT. LEARN IT. LIVE IT.

Dr. Amy's book ***"Feel Good Nutrigenomics Your Road Map to Health"*** will help you understand the basics of methylation. It is available at www.holisticheal.com. Dr. Amy then recommends using the ***Companion Guide***, which provides step by step instructions on how to navigate the protocol. A free copy of this guide can be found on your test results CD or www.scribd.com/dramyyasko.

Knowing how to interpret your genetic results is an important first step in taking charge of your health. Use this Methylation Pathway Analysis program (MPA), the Companion Guide, and Dr. Amy's other resources to help determine how to best implement a customized supplement plan that is right for you.

With love, hope, & wishing you good health always
Dr. Amy

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To follow the Program please use the Companion Guide enclosed on your CD.

Information in this packet is based on the work of Dr. Amy Yasko. Each analysis is processed through a program created by Dr. Amy using her suggestions based on your genetics. Page 22 shows results followed by a list of supports and their associated supplement suggestions.

THE PROGRAM CONSISTS OF THREE STEPS

Step One Overview: See page 15 of the Companion Guide

The first step is basic preparation, which can be done by anyone, no matter what your SNP's are, and whether you know what they are or not. Everyone would benefit from many of the foundational recommendations in this first step. You can also think of Step One as what you do while you wait for your test results, which will allow you to then target support for your own specific SNP's throughout the later steps of this program.

- Focus on a healthy diet, eliminating/limiting excitotoxins (glutamate, glutamine, aspartate, Aspartame etc. see list page 86 of the Companion Guide) that contribute to neurological inflammation. Make dietary changes that help to balance the neurotransmitters GABA and glutamate to lower neurological inflammation
- Balance minerals including lithium
- Short Cut supports for BHMT, SHMT, and CBS (based on UAA, taurine and ammonia levels) and ACAT
- Organ supports strengthen the digestive organs to help prepare the body for detox, to support impaired systems and aid the body in repairing and generating new neurons including preferred probiotics

Step Two Overview: See page 60 of the Companion Guide

While continuing to follow many of the recommendations of Step One, you will move on to Step Two, in which you will begin the process of detoxification.

- Supplementing to bypass mutations included in the Long Route, which allows for natural detoxification: MTHFR, MTR, MTRR, AHCY, COMT, MAO A, SUOX, NOS, and VDR

- Supports to address specific gut bacteria.
- As you begin to slowly and gradually introduce the supplements customized to your own SNP's along with long route, you will naturally begin to detoxify. This occurs because supporting the methylation cycle makes detoxification more efficient.

Step Three Overview: See page 77 of the Companion Guide

Once sufficient detox has occurred via the Step Two process, which may take months or even years, you can then begin Step Three, which helps the body remyelinate nerves and enhances nerve function.

- Re-myelination
- New nerve growth
- Maintenance

For those who may not want to do the full Program you can take a look at the Simplified Program at: www.scribd.com

- **If you feel that you cannot even handle the Simplified Program, Dr. Amy believes that everyone, should at a minimum, take at least one All In One Multi-Vitamin, BeCalm spray at night and Black Bear spray in the morning even if you cannot add another supplement. This is based on the very recent article showing that proper methylation prolongs life, lowering ALL CAUSES of mortality. In other words, no matter what you will eventually pass away from, you will live longer if methylation is functioning properly.**

Nutritional Methylation Pathway Analysis

The results of nutrigenomic testing should help to put your mind at ease by giving you suggestions that you can actually act on. Dr. Amy Yasko only believes in genetic testing if it gives you information that translates into positive constructive action. Dr. Amy's personal belief is that genetic testing without any knowledge of how to address issues that are uncovered is unethical. Her ultimate goal is to use the Nutrigenomic testing as a guide to proper supplementation to bypass genetic weaknesses that are uncovered by DNA test results. The purpose of the Methylation Pathway Analysis is to serve as a tool to help you to understand what supplements, herbs and vitamins you can use to bypass weaknesses in a particular nutritional pathway in your body. This supplementation is then followed by regular biochemical testing (i.e. UAA, UTM/UEE, HMT etc.) to monitor progress.

While there are a number of other Nutrigenomic tests available on the market, what is special about this test and analysis is that it comprehensively looks at one pathway, what Dr. Amy calls the "Methylation Cycle". Dr. Amy sees the Methylation Cycle as the intersection of several important pathways in the body, the common point is a need for "methyl" groups. Methyl groups are simply small chemical compounds whose structure is similar to water. Where water is H2O, a methyl group is CH3. The ability to generate and move these groups is critical to health; these groups are needed for a large number of reactions in the body. "Methylation takes place over billion times a second in the body. It is like one big dance, with bio-chemicals passing methyl groups from one partner to another" (The H Factor, Dr. James Braly and Patrick Holford).

One way to think about the difference between this analysis and others is to think of it in terms of a road map. If you wanted to travel from your hometown to Dr. Yasko's hometown in Maine you would need a map with detailed directions. This would be especially important if certain roads along the way were closed due to construction, bridges out because of flooding, or other road detours. It would help to have a detailed map drawn for you that took all of these specific situations into account. Your Nutrigenomic test tells you where the "construction" sites are located, which bridges are out and where detours are on your individualized map. With this knowledge you can put together an analysis that will help you get from your hometown to her hometown in Maine without getting stuck in a ditch or lost on a detour. The more information you have about specific genes in this particular pathway the easier it is to construct your personal map. This is analogous to having the model of your car, knowing how many miles per gallon you get, how often you feel that you need to stop at a rest area and when you need to fill your tank or take a break from driving. With this information you are in a better position to plan your trip. This is different from other tests that may tell you where your hometown is located and where your destination lies on the map, but without any of the specific information between the two points. Without those details, you do not know if the route you may have chosen has been closed, if the bridge is out, or if there is a detour that will add more time to your travel. Given only a starting and stopping point means the rest of the trip is simply guesswork. The Nutrigenomic test and MPA are designed to take the guesswork out of your trip to health and wellness. While other Nutrigenomic tests look at isolated genes in a wide range of pathways, this test is designed to look comprehensively at a very critical pathway in the body and from that construct a personal road map to health and wellbeing. Even if you are missing just a single SNP, it is like missing a critical piece of information, such as a route that is closed for construction.

Before we get to the specific results of your Nutrigenomic test and the supplement suggestions to help you on your road to health and wellness, it is important to understand that most mutations or SNP variations that are revealed are NOT "all or none mutations". In other words, if you or your loved one

has a mutation or a SNP variation, it does not mean that the activity of this gene is completely "off". It may simply mean that it functions at lower efficiency. When you look at the suggested nutritional support, you are working to increase the ability of the entire methylation cycle to run properly, keeping in mind that it has been functioning to some degree in spite of any mutations in particular genes. This is a good opportunity to also explain that a variation or maturation does not always mean a gene is not working at optimal efficiency. Rather, it may sometimes mean that it is working at an increased level. The basic assumption is often made thinking the gene involved is decreased or impaired; however, changes in the DNA sequence can result in an increased activity in the gene. Additionally, changes in the DNA sequence can result in a lack of normal regulation of the gene involved.

Just as the physical location of your hometown and Dr. Amy's hometown will not change on a map, your genetics also will not change over time. For this reason this MPA will serve as a road map for your future. Knowledge of your genetics is like having an ultrasound that allows you to see inside of your own individual DNA and to use this information for prevention of potential health issues. Suggestions that are made may be valid today, as well as next week, next year or ten years from now. Once you slowly implement your supplementation, your body can start to support the mutations, this helps in supporting the Methylation Cycle to function properly. This in turn should help your body to detoxify properly.

However, unlike genetic tests, biochemical tests will change over time. Biochemical testing measures the amount or activity of a particular enzyme or protein from a sample of urine, stool, saliva or hair. Biochemical testing can be used to assess the effect of supplementation on your system. Ideally, the goal is to understand that knowledge is power and knowledge of your genetics, including any mutations, can give you the information you need to make informed decisions on how to supplement and bypass these weaknesses in your system. You can then use biochemical testing (to see what test you should be ordering refer to the Companion Guide) to monitor the progress of your supplementation to bypass your mutations. To see test examples or order a test you can go to www.holisticheal.com/health-tests. To learn more about the testing and what to do visit www.feelgoodbiochem.com.

For those of you who are interested in more in depth information about the Methylation Cycle and the genes involved in this pathway including an understanding of which genes have increased activity, which have regulation problems and those which have reduced activity, Dr. Amy would suggest reading the articles and resources available on her sites. She regularly uploads on www.scribd.com/DrAmyYasko or watching her videos at vimeo.com/DrAmyYasko. Other great information can be found on the discussion group at www.ch3nutrigenomics.com and at www.DrAmyYasko.com/Resources.

Don't forget the Companion Guide is a great tool and will help you move through the protocol. You can also order The Yasko Protocol Starter Packet or A Complete Series of Lectures by Dr. Amy Yasko at www.holisticheal.com.

What makes Dr. Amy Yasko's protocol different?

Dr. Amy's protocol takes into account that each of us is unique and a one size fits all approach to health is not the answer. This program was designed by Dr. Amy Yasko, with a background in both integrative healthcare as well as more traditional training. This program has been successfully used to help support complex health conditions such as autism and chronic fatigue syndrome. This program takes into account genetic weaknesses as well as the role played by the environment and infectious agents in developing a tailored plan to keep you on the road to health.

Your individualized roadmap

It has been Dr. Yasko's experience that most health conditions in society today are ***multifactorial conditions***, meaning that a number of circumstances need to go awry simultaneously for non-ideal health to manifest. Multifactorial conditions stem from underlying genetic susceptibility combined with assaults from environmental stressors and infectious agents. Basic parameters like age and gender, along with other genetic and environmental factors play a role in the onset of non-ideal health. Infections combined with excessive environmental burdens often lead to problems with health if they occur in individuals with the ***appropriate genetic susceptibility***.

Personalized nutrigenomic screening

One clear, definitive way to evaluate the genetic contribution of multifactorial conditions is to take advantage of new methodologies that allow for personalized genetic screening. Currently, tests are available to identify a number of underlying genetic changes in an individuals' DNA.

The field of **Nutrigenomics** is the study of how natural products and supplements can interact with particular genes to decrease the risk of disease. By looking at changes in the DNA in these nutritional pathways it enables one to make supplement choices based on their particular genetics, rather than using the same support for every individual regardless of their unique needs. A knowledge of imbalances in nutritional genetic pathways allows one to utilize combinations of nutrients, foods and natural ribonucleic acids to bypass mutations and restore proper pathway function.

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The ***methylation cycle*** is a central pathway in the body that is particularly amenable to nutrigenomic screening for genetic weaknesses. The result of decreased activity in this pathway causes a shortage of critical functional groups in the body called ***methyl groups*** that serve a variety of important functions.

Your body's personal mechanic

While the term may seem intimidating, a *methyl* group is actually just a group of small molecules, similar in size to the water molecule (H2O). Water is a key to life as are methyl groups critical for health and wellbeing. Methyl groups are simply "CH3" groups; they contain 'H' like in water and a 'C' like in coal or diamonds. However, these very basic molecules serve integral functions; they are moved around in the body to turn on or off genes.

One way to look at the role of methyl groups is that they serve as your own personal *mechanic* for your body, helping to repair and direct functions in your body. If we think about your body like a car then let's assume that you have just one car that you need to maintain over the course of your life, with the help of your own personal *mechanic*. The longer you have that car the more outdated it will become. Over the course of a lifetime the car body will accumulate rust and can rot out. Tires may wear out, the engine may need an overhaul. Alternatively the problems may be simpler such as the need for more wiper fluid or simply to keep the car filled with gas and to change the oil. In any case your personal *mechanic* ensures that your car keeps running, that it can stay on the road...in this case on the road to health. If however your *mechanic* is unable to function, then all of these issues will start to accumulate over the course of the lifetime of your car. The rust may get so bad that car components fall off like your muffler or the tires become so worn that it is impossible to navigate a turn without the fear of blowing a tire. In the absence of your *mechanics* function you have no way to repair all of the large and small problems that arise with your car to the point where your car can no longer function.

You can start to see why the proper functioning of the pathway that serves to direct your genes is so important. In addition to the editing of genes, this pathway also serves more direct roles in your body and is thus critical for overall health. While there are several particular sites in this pathway where blocks can occur as a result of genetic weaknesses, thankfully supplementation with appropriate foods and nutrients can help to bypass these mutations to allow for restored function of this pathway.

By testing to look at mutations in the DNA for this methylation cycle it is possible to draw a personalized map for each individual's imbalances which may impact upon their health. Once the precise areas of genetic fragility have been identified, it is then possible to target appropriate nutritional supplementation of these pathways to optimize the functioning of these crucial biochemical processes.

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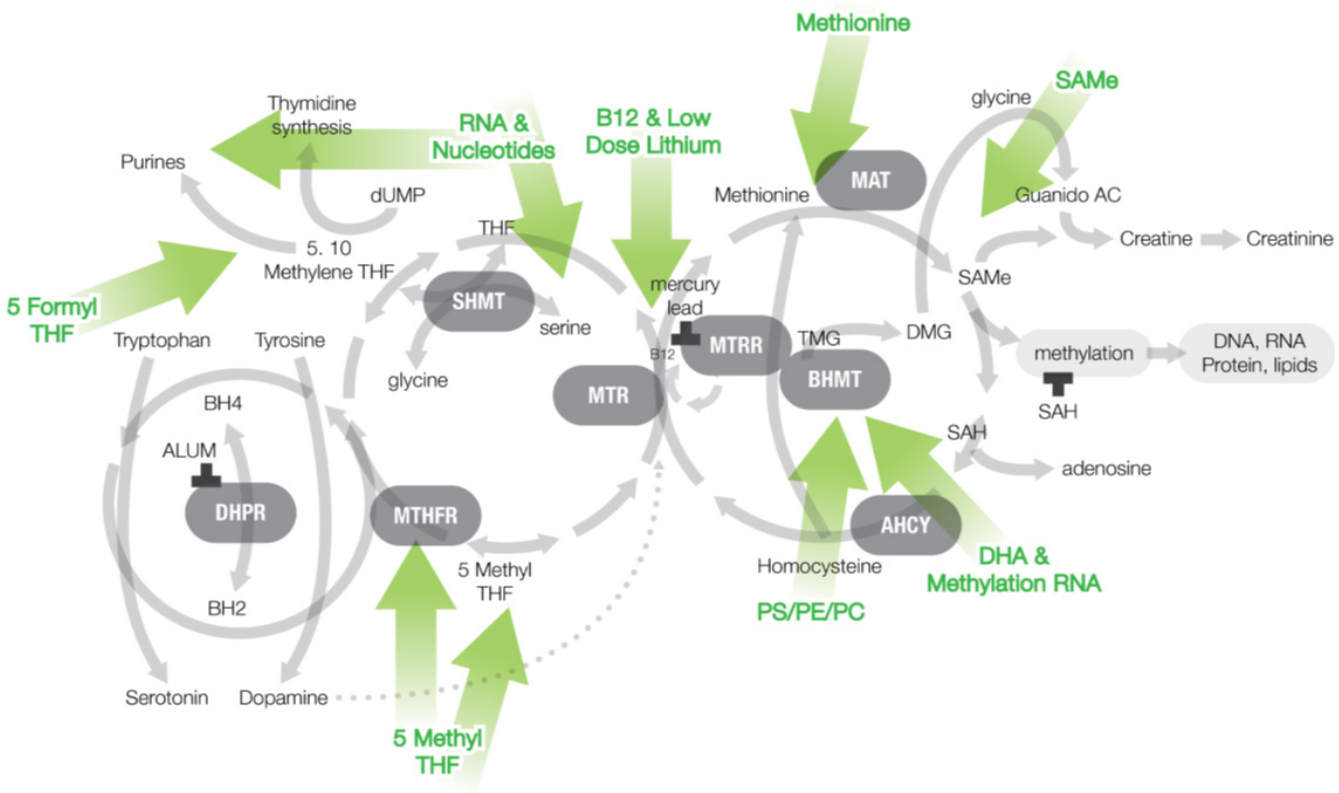
As seen in the ***diagram*** below there are specific places in the cycle where support can be added. This support helps to bypass mutations in the pathway in a similar manner to the way you might take a detour on a highway. We can look at mutations in this pathway as analogous to a collision that has totally shut down traffic going in one direction on a highway. Support to bypass mutations in this pathway is like taking an alternate route to avoid the accident on the highway. Thus, the use of key nutrients or foods can aid in helping to bypass methylation cycle mutations and help restore function to this pathway.



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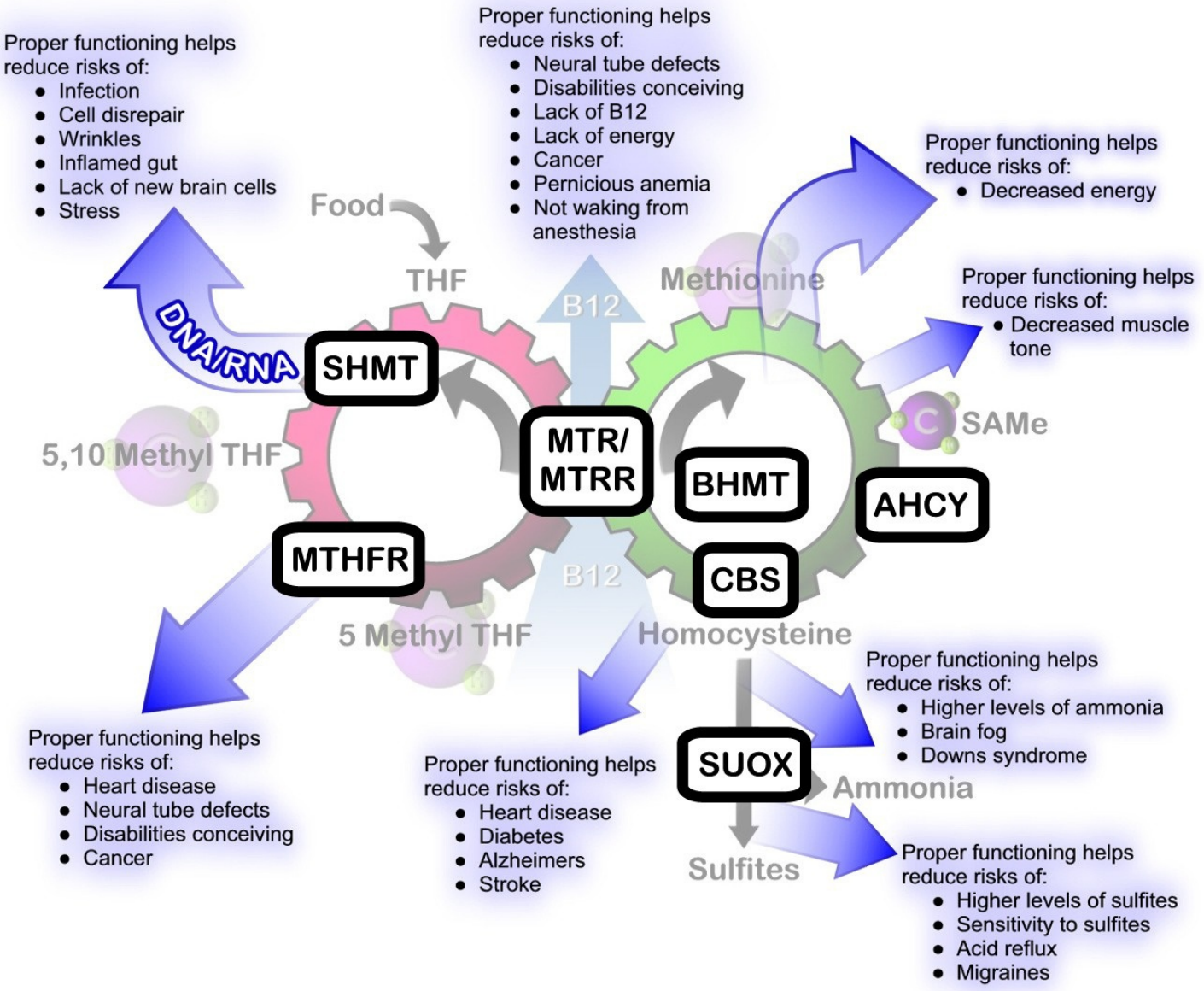
Description of Genes

The following is a very brief description of the genes that are included in this nutrigenomic panel, including information to help you to understand why it is important to look at nutritional supplementation for any imbalances in the body. Again, for those who would like more detailed and comprehensive information, consider reading the books, workbook, articles and other resources available online at www.scribd.com/DrAmyYasko as well as joining the discussion group at www.ch3nutrigenomics.com.



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COMT *(catechol-O-methyltransferase)*:
A primary function of this gene is to help to break down dopamine. Dopamine is a neurotransmitter that is recognized for its role in attention, language, as well as reward seeking behavior. Dopamine helps to cause pleasurable feelings that aid in reinforcing positive behaviors and motivating individuals to function in certain reward gaining activities. COMT is also involved in the breakdown of another neurotransmitter, norepinephrine. The balance between norepinephrine levels and dopamine levels has been implicated in ADD/ADHD; in addition, dopamine levels are important in conditions such as Parkinson's disease. COMT is also involved in the proper processing of estrogen in the body. Sensitivity to pain has recently been found to be correlated with COMT activity, such that COMT + + individuals may be more sensitive to pain. Methyl B12 may be tolerated better by those with results of - - as compared to those who are ++ or +-.

VDR/Taq and VDR/Fok *(vitamin D receptor)*:
The panel looks at more than one portion of the vitamin D receptor, the Taq as well as the Fok sites. While the Fok change has been related to blood sugar regulation, changes at Taq can affect dopamine levels. For this reason it is important to look at the composite of the COMT and VDR/Taq status and make supplement suggestions based on the combined results at these two sites. The focus on changes in the Fok portion of the VDR is in regards to supplements that support the pancreas and aid in keeping blood sugar in the normal healthy range. Understanding of the VDR SNPs is a bit more complicated.

The situation with Fok is more complex as the polymorphism (FF, loss of site) actually leads to the production of a protein with *increased* activity. The Fok SNP, situated in exon 2, gives rise to an alteration in the start codon position resulting in a 3 amino acid longer protein than produced by the F allele. So the Fok site affects the protein directly such that those who are missing the restriction site (FF) make a shorter protein, but one that is actually more active. While those who do not have a 'mutation' and have the restriction site actually make the full length protein but it has *less* activity. (Nutrition Reviews, What Are the Frequency, Distribution, and Functional Effects of Vitamin D Receptor Polymorphisms as Related to Cancer Risk? Nicholas J. Rukin August 2007(II): S96 -S101Vol. 65, No. 8). In conclusion, the Fok polymorphism yields a 424 VDR variant somewhat more active than the 427 variant in terms of its transactivation capacity as a transcription factor. (Uitterlinden et al. / Gene 338 (2004) 143-156)

The Taq and Bsm situation is even more complicated. Both are in a regulatory portion of the protein and the SNP changes do not affect the protein per se but they both affect a regulatory string of A's in the sequence. Thus the presence or absence of the Bsm and Taq sites affects the number of A's in the protein.

Since Bsm and Taq have inverse effects both Bt and bT impact the number of A's. The number of A's in turn affects the stability of the information to make the VDR protein. As with everything else related to VDR, there is disagreement whether the shorter stretch of A's (Bt) or the longer stretch of A's (bT) grants more stability to the protein. Reports regarding which genotype is associated with a range of diseases or health conditions vary depending on the researcher.

We use the tt or TT designation to denote VDR Taq and FF and ff for Fok. Those who are tt should consider more limited methyl donors. Those who are TT tend to have a greater tolerance for i.e. methylB12. Again, the bottom line is that Dr Amy feels low dose vitamin D plus rosemary and sage and resveratrol are a positive for all. This is especially true as there is conflicting literature regarding disease susceptibility and the various VDR SNPS that at times is totally contradictory.

BHMT *(betaine homocysteine methyltransferase)*:
The product of this gene is central to the "short cut" through the methylation cycle, again helping to convert homocysteine to methionine. The activity of this gene product can be affected by stress, by cortisol levels and may play a role in ADD/ADHD by affecting norepinephrine levels. Those who are BHMT + may benefit from additional short cut support.

AHCY 1,2,19 *(S adenosylhomocysteine hydrolase)*:
AHCY is the enzyme that converts s adenosyl homocysteine (SAH) to adenosine and homocysteine. Decreased AHCY activity should lead to lower levels of homocysteine. Studies using animals with no CBS function suggests that the relationship between CBS enzyme activity, homocysteine levels and SAH and SAMe levels may not be as simple or predictable as one might expect from pathway diagrams. In addition, both SAH and SAMe have been found to affect CBS activity and SAH is known to inhibit methyltrasferase reactions. Also the level of homocysteine affects SAH levels such that higher levels of homocysteine can increase SAH. Clearly, the relationship between these intermediates appears to be complex. (PNAS 2008, 103:17; Theorectic Biology and Medical Modelling 2008, 5:8; JBC 2002, 277:41; Jnutrition 2002,132) It may be especially important for those with AHCY mutations to monitor amino acid levels in order to balance the effects of AHCY mutations, CBS up regulations and other methylation cycle mutation on the system. Run biochemical tests to monitor levels of SAMe and SAH maybe particularly useful. Preliminary data suggests those who are AHCY ++ may benefit from additional SAMe.

CBS *(cystathionine-beta-synthase)*:
The CBS enzyme basically acts as a gate between homocysteine and the downstream portion of the pathway that generates ammonia in the body. The types of CBS mutations that are identified on this

SNP panel cause this "CBS gate" to be left open, this "open gate" is not a neutral situation. The "open gate" can allow support that is added for the rest of the methylation pathway to be depleted, including any B12 that is used to address MTR and MTRR mutations. While there are some positive end products that are generated via the downstream portion of the pathway such as glutathione and taurine, there are also negative byproducts such as excess ammonia and sulfites. By virtue of increased CBS activity, these sulfur groups that were complexed as part of the methylation cycle can now be released into the system as sulfites which are toxic to the body and put an additional burden on the SUOX gene product.

Those who are CBS + may tend toward excessively high taurine levels on a urine amino acid (UAA) test once methylation support is in place. Until adequate support for the methylation cycle is in place the impact of the CBS SNP is often not seen. As Dr Amy described before you can think of the CBS SNPs as a leaky plug in a bath tub. Until you fill the tub with water you cannot tell that the drain plug isn't sealing properly and is causing the tub water to flow down the drain instead of filling the tub. In a similar fashion, you cannot see the impact of the CBS SNP until you have sufficient methylation support in place such that the cycle is filling and at that point the taurine levels will rise well above the 50th percentile on a UAA if more CBS support is needed. Work with your doctor to use follow up UAA testing to monitor taurine levels and use the CBS RNA ONLY as needed to keep taurine in balance as determined by regular UAA testing for taurine levels and as always work in conjunction with your doctor.

SUOX *(sulfite oxidase)*:
This gene product helps to detoxify sulfites in the body. Sulfites are generated as a natural byproduct of the methylation cycle as well as ingested from foods we eat. Sulfites are sulfur based preservatives that are used to prevent or reduce discoloration of light-colored fruits and vegetables, prevent black spots on shrimp and lobster, inhibit the growth of microorganisms in fermented foods such as wine, condition dough, and maintain the stability and potency of certain medications. Sulfites can also be used to bleach food starches, to prevent rust and scale in boiler water that is used to steam food, and even in the production of cellophane for food packaging. The Food and Drug Administration estimates that one out of a hundred people is sulfite-sensitive, and five percent of those also suffer from asthma. A person can develop sulfite sensitivity at any point in life. Because many reactions have been reported, the FDA requires the presence of sulfites in processed foods to be declared on the label.Scientists have not pinpointed the smallest concentration of sulfites needed to trigger a reaction in a sulfite-sensitive person. Difficulty in breathing is the most common symptom reported by sulfite-sensitive people. Sulfites give off the gas sulfur dioxide, which can cause irritation in the lungs, and cause a severe asthma attack for those who suffer from asthma.

Responses in the sulfite-sensitive person can vary. Sulfites can cause chest tightness, nausea, hives and in rare cases more severe allergic reactions. Mutations in SUOX may be a risk factor for certain types of cancer, including leukemia. Do to the complication of the data base norm for this SNP we will note in the Call letter if you need support or not.

SHMT *(serine hydroxymethyltransferase)*:
This gene product helps to shift the emphasis of the methylation cycle toward the building blocks needed for new DNA synthesis and away from the processing of homocysteine to methionine. While DNA building blocks are important, mutations which affect the ability to regulate this gene product and interfere with the delicate balance of the methylation cycle may cause accumulations in homocysteine as well as imbalances in other intermediates in the body, as well as diverting and thus draining methylation cycle intermediates.

NOS *(nitric oxide synthase)*:
The NOS enzyme plays a role in ammonia detoxification as part of the urea cycle. Individuals who are NOS + + have reduced activity of this enzyme. NOS mutations can have additive effects with CBS up regulations due to the increased ammonia that is generated by the CBS up regulations. In addition MTHFR A1298C ++ status may put an additional burden on proper urea cycle function.

MAO A *(monoamine oxidase A)*:
MaoA is involved in the breakdown of serotonin in the body. Like dopamine, serotonin is another neurotransmitter in the body. It is involved with mood, and imbalances in serotonin levels have been associated with depression, aggression, anxiety and OCD behavior. Since Mao A is inherited with the X chromosome and is considered a dependent trait it may not show standard inheritance characteristics in males. Since the X chromosome in males can only come from the mother, this means that the fathers Mao A mutations (or lack thereof) does not play a role in their son's Mao A status. For females, since one X chromosome is inherited from each parent, the genetics tend to reflect the Mao A status of both parents.

ACAT *(acetyl coenzyme A acetyltransferase)*:
ACAT plays a role in cholesterol and other lipid balance in the body, helping to prevent the accumulation of excess cholesterol in certain parts of the cells in the body. ACAT is also involved in energy generation in the body. It is involved in helping to allow protein, fats and carbohydrates from food to be converted into an energy form that can be used by your body. In addition, lack of ACAT may also cause a depletion of B12, which is needed for the "long route" around the methylation cycle.

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ACE *(angiotensin converting enzyme)*: ***Considered for all - No longer testing.***

Changes can occur that affect the activity of the ACE gene that can lead to elevated blood pressure. In animal studies imbalances in this pathway were also correlated with increased anxiety and decreases in learning and memory. Increased ACE activity can also throw off the essential mineral balance in your system due to decreased excretion of sodium in the urine and increased excretion of potassium in the urine. This reaction is also tied to the stress response such that situations of chronic stress can result in additional sodium retention and increased potassium excretion. This excess potassium is excreted provided that the kidneys are functioning properly. In the event that kidney function is compromised, it can lead to the retention of potassium in the body. ACE is a deletion, it is not a SNP. As a consequence it does not associate in the same manner that the other single nucleotide polymorphisms (SNP) on this panel do, so the inheritance pattern of the ACE deletion may not distribute in the same manner as single base changes. If you are on medication for blood pressure you should talk to your doctor before taking any supplements and as always we recommend you work with your doctor.

MTHFR *(methylenetetrahydrofolate reductase)*:

The MTHFR gene product is at a critical point in the methylation cycle. It helps to pull homocysteine into the cycle, serving to aid in keeping the levels in a normal healthy range. Several mutations in the MTHFR gene have been well characterized as increasing the risk of heart disease, as well as cancer, and may play a role in the level of the neurotransmitters serotonin and dopamine.

MTR/MTRR *(methionine synthase/ methionine synthase reductase)*:

These two gene products work together to regenerate and utilize B12 for the critical "long way" around the methylation pathway, helping to convert homocysteine to methionine. High levels of homocysteine have been implicated as risk factors in a number of health conditions including heart disease as well as Alzheimer’s disease. As is the case for COMT and VDR Bsm/Taq, the MTR and MTRR composite status is also important. Mutations in MTR have been reported to increased the activity of this gene product so that it leads to a greater need for B12 as the enzyme is using up B12 at a faster rate. However there are also publications that suggest the A66G mutation in MTR decreases the activity of the enzyme. Based on what is observed clinically in terms of low lithium for those who are MTR+, the former interpretation is more likely. Regardless of which theory is correct, over activity depleting the cycle of B12, or lack of activity impairing the function of the Methylation cycle at that point, the end results is the same in terms of suggestions of supplementation. Those who are MTR + should consider closely monitorning lithium levels.

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Getting Started with Methylation Support:

Once you have added top step one supplements, balanced Gaba/Glutamate and other minerals, it's time to get started with Methylation supports. Although the ultimate goal is to get the long route around the cycle working, this can cause excretion of toxins from the body. While detoxification is a good thing, it can also allow for symptoms during the detoxification process. For that reason, getting the cycle moving by supporting the short cut helps to restore methylation function while limiting detox reactions. Once the short cut is working, and lithium is in balance then B12 can be gradually increased and finally MethylMate A + B (or equivalent source of 5 methyl THF, low dose folinic, nucleotides, lactoferrin, biopterin, phospholipids). *While there are soy free options for PS/PC Dr. Amy prefers the use of PS/PE/PC with PI (Phosphatidylinositol) whenever possible rather than just using a soy-free PS + PC.*

For short cut support consider:

- All in One Multi-Vitamin
- PS/PE/PC (with PI) and SAMe (If tolerated)
- *Soy free PS if a non soy form of PS is required along with a separate source of PC (Seriphos)*
- Vita Organ as a secondary source of PS and to help with nutrient absorption and gut pH
- Daily DHA
- A few drops Methylation RNA
- BeCalm Spray

Lithium not only plays a role in mood, glutamate control and limiting aggression, but also has been shown to be involved in B12 transport. Many adults as well as individuals who are MTR A2756G + tend to have lower levels of lithium as judged by hair metal analysis (HMT). Supporting with higher levels of B12 before having ascertained that lithium is in balance may lead to further depletion of lithium levels. For this reason Dr.Yasko highly suggests running a hair metal test (HMT), and/or blood lithium test along with a urine essential element test (UEE) to assess the lithium level in the system. If lithium levels are low in hair and blood or urine, or if very high level lithium excretion (in the absence of support is seen in urine) consider additional lithium supplementation with your doctor before moving on to B12 support. Sources of lithium support can include BeCalm Spray, low dose lithium orotate, and All in One Multi-Vitamin. The level of support needed should be determined by a combination of running biochemical tests (UEE, HMT, blood lithium) as well as consultation with your health care provider.

Work on increasing B12 while continuing to follow lithium to be sure it stays in balance with increasing B12. Running HMT several times a year can help monitor lithium levels with increasing B12 support.

Determine Your Ideal Form of B12

Once your lithium levels are in balance and short cut support is in place it is time to start to increase B12 support and to customize your supplement plan to optimize your health, based on your personal results. Just as the GPS system in your car guides you in unknown areas when you are driving, so too can your nutrigenomic results guide you in individualizing your personal healthcare. Not all of us can tolerate caffeine. We all know people who can drink espresso just before bed and fall asleep like a baby and others who are shaking from a single cup of dilute coffee. These differences in part reflect individual tolerances to certain compounds in coffee. These effects are similar to the response people can have to different forms of B12. We need B12, it is a critical B vitamin and by now all of you are getting some low dose B12 support from the All in One Multi-Vitamin and Ultimate B complex. The forms of B12 in those vitamins are designed to be tolerated by all, but now it is time to add some specific B12 based on your nutrigenomic results. The chart below will help you to determine which form of B12 might be best tolerated by your system. There is a more detailed description of the types of B12 along with references for their use after the chart if you want more information than simply knowing which type of B12 might be best suited based on your nutrigenomics.

COMT V158M	VDR Taq	B12 types that should be tolerated
- -	++ (TT)	All three types of B12
--	+- (Tt)	All three types with less methyl B12
--	-- (tt)	Hydroxy B12 and Adenosyl B12
+-	++	All three types with less methyl B12
+-	+-	Hydroxy B12 and Adenosyl B12
+-	--	Hydroxy B12 and Adenosyl B12
++	++	Hydroxy B12 and Adenosyl B12
++	+-	Hydroxy B12 and Adenosyl B12
++	--	Mostly Hydroxy B12

While this chart helps to guide you on the choice of the type of B12 based on nutrigenomics, it is also important to pay attention to what your body is telling you. In spite of nutrigenomics if you are having trouble tolerating methylB12 then listen to your body and use hydroxyl with some adenosyl B12 instead. This is particularly true for adults who often have a more difficult time with any supplements that can trigger detox including any methyl B12 support.

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Ph.D, NHD, AMD, FAAIM, HHP, CTN

Why it is so important to have a form of B12 that you can tolerate

Vitamin B12 is a water soluble vitamin. This means that it doesn't stay in the body for a long period of time and that more frequent support with B12 may be needed to maintain healthy B12 levels in the body.

- Vitamin B12 is important for energy, for balance related sports, for endurance sports, for healthy red blood cells, for memory, among other roles in the body.

- Vitamin B12 can be depleted by drinking alcoholic beverages, a poor diet, certain medications and as we age.

- Lack of B12 has been associated with fatigue, alcoholic liver disease, anemia, cancer, ulcers, dementia, neural tube defects, depression and memory loss.

- Higher levels of B12 correlate with improved balance, energy, and endurance in athletics.

Different types of B12 work best for different people

Vitamin B12 also called cobalamin can include hydroxyl B12, methylB12, cyanoB12 and adenosylB12. Many vitamins, including B12, are not active in the form in which they are normally found in food, instead the body needs to convert the B12 into a form that it can use directly. B12 is needed for the proper functioning of a number of different enzymes in the body, however not all types of B12 are equal and not all types of B12 can be easily changed to what is needed for critical reactions in the body. Hydroxy, methyl and adenosyl are all forms of B12 that are used directly by reactions in the body. CyanoB12 must be converted for use in the body and as the name suggests, cyanocobalamin contains a cyanide molecule.

- **Methyl B12** can be used in the body, though it cannot be tolerated by everyone. Those who get jittery from caffiene, coke, or tea may not react as well to methyl B12. Many adults don't do as well with methyl B12 in spite of their nutrigenomics and so it is fine to choose an alternate form

- **Adenosyl B12** is a special form of B12 that is important in the energy cycle in the cells of your body. It is important to have adenosyl B12 but it is not as versatile as other forms of B12 so it can be used in lower doses.

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- **Hydroxycobalamin**, or hydroxyB12 is a unique form of vitamin B12, which is more easily converted to the form that is actually used for reactions in the body. This might cause you to ask, why doesn't everyone use high dose hydroxylB12 in their formulations? Well, Hydroxycobalamin (Hydroxy B12) is more difficult to work with, harder to keep in an active form and more expensive than some other forms of B12, such as cyanoB12. For this reason, many other products do not contain hydroxyl B12 and instead use cyanoB12.

- **CyanoB12** contains a cyanide molecule. So when you take cyanoB12 your body must first turn it into hydroxyB12 in order to use it, and then must find a way to get rid of the toxic cyanide molecule. We all know cyanide is a poison even if the rest of the B12 molecule is good for you. The body actually uses up hydroxyB12 in order to detoxify cyanide. So, not only is cyanoB12 not the form your body ultimately needs, but taking higher doses of cyanoB12 may actually deplete your stores of hydroxy B12. So why would anyone use cyano B12 if it can be toxic? Well, in low doses it may be helpful for the eyes, but for the most part cyanoB12 is used because it is much less expensive, and a form of B12 that is easier to keep stable.

Options for additional B12 support:

- All in One Multi-Vitamin
- Hydroxy Mega Drops
- Get B12 Spray
- Black Bear Spray
- Black Bear Drink
- Adenosyl
- Methyl Mega Drops
- B12 Injections (if possible Hydroxy B12)
- Dibencozide (adenosyl B12) tablets
- Perque Activated B12 Guard
- Low dose more limited support with cyano B12 (as long as hydroxyl support is also in place)
- B12 gum
- B12 patch

For a complete list of B12 support:
http://www.holisticheal.com/complete-b12-list.html

The remainder of long route support

In addition to B12 support the long route around the cycle also uses folate. Those with MTHFR mutations cannot use plain folate ideally, and instead the use of 5 methyl THF helps to bypass MTHFR mutations. MethylMate B is a liquid form of 5 methyl THF that allows you to adjust the dose of 5 methyl THF down to very low levels. This is important as the addition of 5 methylTHF will often be the piece that triggers significant detox of toxic substances from the body. Having the ability to adjust this process with exquisite control is a real plus as it allows you to adjust the dose of 5 methylTHF and hence to have some control over the rate of detox.

Starting with one drop or even one dilute drop is possible and then gradually increasing to 3 drops daily if tolerated. Dr. Amy is well aware that there are other programs that use much higher doses of 5 methyl THF. While this is not her preference at all, you can increase the amount of MethylMate B as needed to adapt to whatever program you are using.

MethylMate A contains the ingredients to help to support the remainder of the methylation cycle. It includes nucleotides to take the pressure off the cycle and the immune system for generating nucleotide building blocks. It includes a low dose source of folinic acid as well as lactoferrin to support proper balance for the SHMT portion of the cycle (although those who are SHMT + should consider additional SHMT support). MethylMate A also includes low dose support for natural biopterin, as well as additional short cut support for PS, PE, PC, PI. One or more MethylMate A is sufficient for support of the cycle.

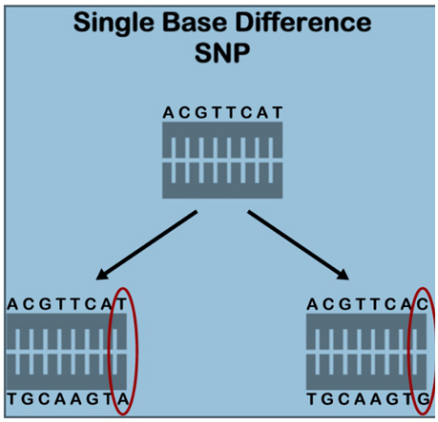
The new All in One Multi-Vitamin also contains very low levels of the nutrients for long route support. (The doses in the All in One have exceedingly low levels of these nutrients, just enough to allow for support without possible detox that can occur with higher doses.) Think of All in One Multi-Vitamin as the gas in the reserve tank in your car. Ultimately you need to fill that tank with gas for a long trip. However, just having a few gallons in your reserve tank will at least allow you to drive home from the market without running out of gas.

What Exactly are SNPs?

While the first step that emerged from the Human Genome Project has been to identify genes associated with a particular health conditions, the next step is to use this information to look for the presence of these identified disease causing genes in an individual person. Rather than looking at complete gene profiles, it is also possible to look at particular changes in the "spelling" of your DNA in only specific areas of interest. In this way, you can more quickly get a sense of known genetic

weaknesses. Companies that offer this service enable you to look at genes of interest that may affect your susceptibility to heart disease, inflammation, detoxification or simply your ability to absorb nutrients. These tests are available using saliva samples, cheek swabs as well as blood samples.

In order to find relationships between genetic changes and the susceptibility to health conditions this testing is done utilizing single nucleotide polymorphisms, otherwise known as SNP's (pronounced snips). This process systematically compares genomes of those individuals with health conditions to the corresponding DNA of a "normal" population. To identify a SNP is a very arduous and time consuming process as there may be 400 or more genes in a shared region, making it difficult to identify changes and trends. However, once it has been identified, making practical use of this information is quick and straightforward.



How to Read the Nutrigenomic Test

There are two copies of each gene that we are looking at in the profile. One copy comes from each parent. When both copies have a particular SNP or mutation, in other words when both copies are identical, either + + or - - it is called "**homozygous**". When you have one copy that is + for the change and the other is - for the change it is called "**heterozygous**." The + and - designations themselves refer to whether or not the gene has a change from what is considered the **norm**. If there is a change from the **norm** then it is termed as +. No change is designated by a - sign. The definition of what is the **norm** can vary from lab to lab. It will depend in part on what the lab uses as a reference database. This is why you are also given the **call letter** for each SNP. The call letter tells you what base was seen by the lab at a precise location on the gene.

For instance, when we look at the MTHFR gene, and the particular SNP we are interested in is the C677T. The lab is looking at position 677 in the DNA for a change from a C to a T. If there is a change then the call letter will show a T and the designation will be +. If there is no change then the call letter will be C and the designation will be -. If a different lab considers the change to a T as the **norm**, than

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they might show a T in position 677 as a -, as their reference database may feel that it is normal to have a T in that position. This is why the **call letter** is so important. In cases where there is a discrepancy from one lab to another the actual **call letter** will let you know what base was seen at a precise location. This enables you to be certain that tests run from different labs gave the same actual experimental result even if their reference standard for a **norm** was different.

Assume the following scenario as an example Dr Amy, is 5 feet 3 inches tall. That is equivalent to the call letter in this analogy. It is a precise measurement. If she compares her height to that of her children she is taller than one of her girls, the same height as one and shorter than one of them. Using her daughters as a reference base Dr Amy would consider her own height average. However if she compares her height to that of the rest of the population of her home town she is actually quite short. Many of the individuals in her town are very tall. Using the + + and - - designations she might be + - if her reference norm was her own girls or + + if reference database was Dr. Amy's hometown. In either event her height, by precise measurement is 5' 3" and that will not change. Knowing the lab value allows her to compare her height to other databases in the future.

For the results of your test you can use the following guide:

Minus "-" represents no mutation (norm).
Plus "+" represents a mutation (not the standard norm).
"-/-" indicates there is no mutation (Homozygous).
"+/-" indicates there is one mutation (Heterozygous).
"+/+" indicates there is a double mutation (Homozygous).

Please note: The results column is color coded to correspond with the level of the support needed, so you may see some +/- in red. For questions on the protocol please refer to the discussion group at www.ch3nutrigenomics.com. To find out what mutations you should be supporting first please refer to the workbook.

- A red background indicates a greater level of support is needed.
- A yellow background indicates that support is needed, but to a lesser degree than red.
- A green background indicates that there is little to no support needed.
- A blue background indicates a result was reached by looking at multiple SNPs in combination.

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BioMedical ID: 19261
Doe, John

Test Kit Number: 48
Test Type: MPA
DOB: 8/15/1980

Collection Date: 9/11/2013
Processed Date: 10/10/2013

Conditions:
Condition Note:

The left color coding is an effort to streamline our protocol and further your understanding of your genetic test results, we have devised a color-coding system that includes each gene. This color-coding system is meant to serve as a visual reference to help you better navigate the Methylation Pathway Diagrams, compounded supplements, and mutation specific Nucleotide Blends.

SNP	Gene	Variation	Result	Call
RS4680	COMT	V158M	-/-	G
RS4633	COMT	H62H	-/-	C
RS769224	COMT	61	-/-	G
RS731236	VDR	Taq	Tt	Hetero
RS2228570	VDR	Fok	FF	C
RS6323	MAO A	R297R	-/-	G
RS3741049	ACAT	1-02	+/-	Hetero
RS1801133	MTHFR	C677T	-/-	C
RS2066470	MTHFR	3	+/-	Hetero
RS1801131	MTHFR	A1298C	+/+	C
RS1805087	MTR	A2756G	-/-	A
RS1801394	MTRR	A66G	+/+	G
RS10380	MTRR	H595Y	-/-	C
RS162036	MTRR	K350A	-/-	A
RS2287780	MTRR	R415T	-/-	C
RS2303080	MTRR	S257T	-/-	T
RS1802059	MTRR	11	+/-	Hetero
RS585800	BHMT	1	-/-	A
RS567754	BHMT	2	+/-	Hetero
RS617219	BHMT	4	+/-	Hetero
RS651852	BHMT	8	+/+	T
RS819147	AHCY	1	-/-	A
RS819134	AHCY	2	-/-	T
RS819171	AHCY	19	-/-	A
RS234706	CBS	C699T	+/-	Hetero
RS1801181	CBS	A360A	+/-	Hetero
RS2298758	CBS	N212N	-/-	C
RS773115	SUOX	S370S	-/-	No Support Needed
RS1979277	SHMT	C1420T	+/+	A
RS1799983	NOS	D298E	-/-	G

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List of Supports and their associated Supplement Suggestions.

Please note If a supplement Is listed For more than one support, please take only one recommended dose Of that supplement. If just starting out please refer To the Companion Guide And start one supplement at a time And work up To the full dose. The Companion Guide will also Let you know In what order you should be starting Each support.

As always defer To your doctor before Using supplementation And On final dosages.

Support	Result	Supplements	Dosage	Your Checklist
TOP STEP ONE/ Nutritional Groundwork		All in One Multi-vitamin	1-4 daily	_____
		MTHFR A1298C+ Liver Support Cap	1-2	_____
		VDR Fok/Pancreatic Cap	1	_____
		Ultimate B Complex	1-2	_____
		Zinc Lozenges	15-40 mg	_____
		Ora-Kidney	1	_____
		Cod Liver Oil	1	_____
		Special Digestive Enzymes	3x/day 1/w each meal	_____
		Resveratrol Spray	1 or more sprays	_____
		BeCalm Spray	2 or more sprays	_____
		Vita D-Light Spray or Vitamin D	1 or more	_____
		Adrenal Concentrate (Formerly Ora-Adrenal-80)	1	_____
		VitaOrgan	1 or more	_____
		GABA	1 or more	_____
		Vitamin C	500mg to 1000mg	_____
		Probiotics- several types-rotate daily		_____
		Cell Food	2 drops	_____
		BioNativus Trace Minerals	2 drops	_____
		Run UEE & HMT to Determine Mineral Support		_____
		General Support Nucleotide	3-5 drops or more as needed	_____
		Bowel Support Nucleotide	3-5 drops or more as needed	_____
		Cytokine Balance Nucleotide	3-5 drops or more as needed	_____
		Nerve Calm Formula Nucleotide	3-5 drops or more as needed	_____

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Conditions:
Condition Note:

Support	Result	Supplements	Dosage	Your Checklist
TOP STEP ONE/ Nutritional Groundwork		Stress Foundation Nucleotide	3-5 drops or more as needed	_____
		Fatigue Support Nucleotide (CFS Adults)	3-5 drops or more as needed (CFS Adults)	_____
		Pycnogenol	Optional if taking All in One	_____
		Grape Seed Extract	Optional if taking All in One	_____
		Vitamin K (Super K) (In VDR, ACAT, Mitoforce)	Optional if taking All in One	_____
Glutamate/Gaba Balance (see Companion Guide Page 20)		Nerve Calm Formula Nucleotide		_____
		Comfort Support Nucleotide		_____
		BeCalm Spray		_____
		Melatonin Sleep Spray		_____
		Resveratrol Spray		_____
		Progesterone Cream (Pro-Gest Body Cream)		_____
		GABA		_____
		Pycnogenol		_____
		Grape Seed Extract		_____
		Valerian Root		_____
		Jujube		_____
		Lithium Orotate (work with your Doctor)		_____
		Lithium Drops (work with your Doctor)		_____
		Potassium		_____
		L-Theanine		_____
		Taurine (not for CBS + or SUOX mutation)		_____
		Passion Flower (Passiflora spp. Flower & Leaf)		_____
		KuShen Sophora Flavescens		_____
		Relaxation Support		_____
		Zen		_____
Before adding EXTRA B12 check Lithium		If Levels are low in hair, blood or urine or excreting very high levels consider:		_____
		BeCalm Spray	3-5 sprays	_____
		Lithium Orotate (work with your Doctor)	Low dose or Lithium Drops	_____

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Support	Result	Supplements	Dosage	Your Checklist
Before adding EXTRA B12 check Lithium		All in One Multi-vitamin	2-4 daily	_____
BASIC METHYLATION CYCLE SUPPORT: In order listed		All in One Multi-vitamin	1-4 daily	_____
		Phosphatidyl Serine Complex (PS/PE/PC)	1 or more or Pedi-Active or Seriphos	_____
		DHA Neuromins	1	_____
		Methylation Support Nucleotide	3-5 drops	_____
		VitaOrgan	1 or more	_____
		BeCalm Spray	2 or more sprays	_____
		SAM-e (Low Dose in Methyl Max)	(If tolerated)	_____
		MethylMate A Compound	1-2	_____
		MethylMate B Drops	1-3 drops	_____
		Hydroxy B12 Mega Drops	1 or more drops	_____
		Hydroxy B12 Spray (GET-B12)	1 or more sprays	_____
		Black Bear Energy Drink		_____
		Kidney Support Nucleotide	3-5 drops or more as needed	_____
		Liver Support Nucleotide	3-5 drops or more as needed	_____
BASIC ACE SUPPORT FOR ALL		All in One Multi-vitamin	1-4 daily	_____
		ACE + MSF Nucleotide	2 drops or more as needed	_____
		Stress Foundation Nucleotide	3-5 drops or more as needed	_____
		Kidney Support Nucleotide	3-5 drops or more as needed	_____
		Adrenal Concentrate (Formerly Ora-Adrenal-80)	1/2	_____
		Progesterone Cream (Pro-Gest Body Cream)	Low dose	_____
		BASIC METHYLATION CYCLE SUPPORT LIST		_____

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Support	Result	Supplements	Dosage	Your Checklist
COMT V158M (COMT H62H) -- VDR Taq Tt	--/+-	All in One Multi-vitamin	1-4 daily	_____
		COMT V158M -- MSF Nucleotide	3-5 drops or more as needed	_____
		VDR Taq + MSF Nucleotide	3-5 drops or more as needed	_____
		Mood D Nucleotide	3-5 drops or more as needed	_____
		Methyl Max Compound	1/4 cap	_____
		Methyl B12 Mega Drops	1 drop	_____
		Hydroxy B12 Spray (GET-B12)	1 spray	_____
		B12 Methyl Chewable	1	_____
		B12 Hydroxy Chewable	1	_____
		Melatonin Sleep Spray or Melatonin if needed at bedtime		_____
		SAM-e (Low Dose in Methyl Max)	1	_____
		Vita D-Light Spray or Vitamin D	1	_____
		BeCalm Spray	2-4 sprays	_____
		BASIC METHYLATION CYCLE SUPPORT LIST		_____
VDR Fok	FF	All in One Multi-vitamin	1-4 daily	_____
		VDR Fok + MSF Nucleotide	3-5 drops or more as needed	_____
		VDR Fok/Pancreatic Cap	1	_____
		Special Digestive Enzymes	3x/day 1/w each meal	_____
		Vita D-Light Spray or Vitamin D	1 or more	_____
		GABA	1-3 daily	_____
		Watch Chromium & Vanadium levels on UEE		_____
		Chromium Picolinate		_____
		Glucose Support		_____
		Vanadyl Sulfate		_____
		BASIC METHYLATION CYCLE SUPPORT LIST		_____
ACAT 1-02	+/-	All in One Multi-vitamin	1-4 daily	_____
		ACAT + MSF Nucleotide	3-5 drops or more as needed	_____
		ACAT/BHMT Cap	1-2 with each meal	_____

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Support	Result	Supplements	Dosage	Your Checklist
ACAT 1-02	+/-	Adenosyl B12		_____
		GSH Caps	1	_____
		Hydroxy B12 Spray (GET-B12)	1 spray	_____
		Hydroxy B12 Mega Drops	1 drop	_____
		CoEnzyme Q10 Spray and/or Coenzyme Q10 Soft Gels	Extra	_____
		Special Digestive Enzymes	3x/day 1/w each meal	_____
		Riboflavin 5'-Phosphate (Low Dose ACAT/BHMT)	1	_____
		Ribose (in MitoForce, Black Bear Drink, CoEnzyme Q10)	Low dose	_____
		VitaOrgan	1-2 caps	_____
		Red Rice Yeast & CoEnzyme Q10	Low dose	_____
		Biotin & Adenosyl B12	1	_____
		Bile Acid Factors		_____
		BASIC METHYLATION CYCLE SUPPORT LIST		_____

MTHFR 3 MTRR A66G	+/- +/+	MTR/MTRR + MSF Nucleotide	3-5 drops or more as needed	_____
		MTR/MTRR/SUOX Basic Methylation Support/Sulfite Ingestion Cap	1/2 to 1	_____
		All in One Multi-vitamin	1-4 daily	_____
		MTHFR 3 + MSF Nucleotide	3-5 drops or more as needed	_____
		B12 Multiple routes/ forms, support gradually increasing doses over time		_____
		Hydroxy B12 Mega Drops	1 or more drops	_____
		Adenosyl B12		_____
		Methyl B12 Mega Drops (depending on Comt/taq status)	1 or more drops	_____
		Hydroxy B12 Spray (GET-B12)	1 or more sprays	_____
		MethylMate B Drops	1-3 drops	_____
		B12 patch		_____
		B12 Chewable tablets (mix of hydroxyl, methyl, adenosyl depend on Comt/taq status)	as tolerated	_____
		B12 gum (if able to chew gum)	as tolerated	_____
		B12 injections (choice of Hydroxy or Methyl depends on COMT/Taq status)	as tolerated	_____

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Conditions:
Condition Note:

Support	Result	Supplements	Dosage	Your Checklist
MTHFR 3 MTRR A66G	+/- +/+	DMG	After 8 or more weeks of support add 1 to 2 daily	_____
		BASIC METHYLATION CYCLE SUPPORT LIST		_____
MTHFR A1298C	+/+	All in One Multi-vitamin	1-4 daily	_____
		MTHFR A1298C+ MSF Nucleotide	3-5 drops or more as needed	_____
		MTHFR A1298C+ Liver Support Cap	2-3	_____
		MetalAway Cap	1	_____
		Homeopathic BH4	as needed	_____
		Royal Jelly (Only if **NO** bee allergies)		_____
		MethylMate B Drops	1-3 drops	_____
		BASIC METHYLATION CYCLE SUPPORT LIST		_____
MTRR-11	+/-	All in One Multi-vitamin	1-4 daily	_____
		MTRR11 + MSF Nucleotide	3-5 drops or more as needed	_____
		VitaOrgan	1-3 caps	_____
		AminoAssist Cap	1-3 caps	_____
		AminoAssist Spray	2-4 sprays	_____
		Placenta	1-2	_____
		Royal Jelly (Only if **NO** bee allergies)	1-2	_____
		Adrenal Concentrate (Formerly Ora-Adrenal-80)	1	_____
		BASIC METHYLATION CYCLE SUPPORT LIST		_____
BHMT-02 BHMT-04	+/- +/-	All in One Multi-vitamin	1-4 daily	_____
		BHMT 1, 2, 4 + MSF Nucleotide	3-5 drops or more as needed	_____
		VitaOrgan	1-2 caps	_____
		Phosphatidyl Serine Complex (PS/PE/PC)	2 or Pedi-Active Phospha or Seriphos (Soy Free)	_____
		DHA Neuromins	1	_____
		ACAT/BHMT Cap	3	_____
		GSH Caps	1	_____

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NEUROLOGICAL RESEARCH INSTITUTE

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Doe, John

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Conditions:
Condition Note:

Support	Result	Supplements	Dosage	Your Checklist
BHMT-02	+/-	BASIC METHYLATION CYCLE SUPPORT LIST		_____
BHMT-04	+/-			
BHMT-08	+/+	All in One Multi-vitamin	1-4 daily	_____
		BHMT 8 + MSF Nucleotide	3-5 drops or more as needed	_____
		MTHFR A1298C+ Liver Support Cap	1-2 caps	_____
		Hydroxy B12 Spray (GET-B12)	1 or more sprays	_____
		Hydroxy B12 Mega Drops	1 or more drops	_____
		DMG	1	_____
		B12 Hydroxy Chewable	1	_____
		SAM-e (Low Dose in Methyl Max)	if tolerated	_____
		Phosphatidyl Serine Complex (PS/PE/PC)	2 or Pedi-Active Phospha or Seriphos (Soy Free)	_____
		DHA Neuromins	1	_____
		BASIC METHYLATION CYCLE SUPPORT LIST		_____
CBS C699T	+/-	All in One Multi-vitamin	1-4 daily	_____
CBS A360A	+/-	CBS + MSF Nucleotide and/or Ammonia Nucleotide **(before using check taurine levels on UAA)**	3-5 drops or more as needed	_____
		UAA (Urine Amino Acids) Test	Run to determine Taurine & Ammonia	_____
		CBS/NOS/Kidney Cap	Depending on Ammonia level	_____
		Hydroxy B12 Spray (GET-B12)	1 or more sprays	_____
		Hydroxy B12 Mega Drops	1 or more drops	_____
		Black Bear Energy Spray or Molybdenum caps	1 or more sprays	_____
		Limit Sulfur and limited B6 (or P5P)		_____
		Charcoal/Mag Flush (Activated Charcoal/ Magnesium Citrate flushes)	as needed	_____
		Limit Taurine		_____
		BASIC METHYLATION CYCLE SUPPORT LIST		_____

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Support	Result	Supplements	Dosage	Your Checklist
SHMT C1420T	+/+	All in One Multi-vitamin	1-4 daily	_____
		SHMT + MSF Nucleotide	3-5 drops or more as needed	_____
		AHCY/SHMT Cap	1/w each meal	_____
		SHMT Spray	3X/Day	_____
		Ultimate B Complex	1-2 caps	_____
		Lactoferrin (Depending on Iron Levels)		_____
		MethylMate B Drops	Low dose	_____
		BASIC METHYLATION CYCLE SUPPORT LIST		_____

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The Same List, Organized by Supplement and their associated Supports

The following section is the same list of supplements but put in alphabetical order per supplement with the supports listed to the side. We still recommend you refer to the Companion Guide.

Supplement		Supports				
ACAT + MSF Nucleotide	+/-	ACAT 1-02				
ACAT/BHMT Cap	+/-	ACAT 1-02	+/-	BHMT-02	+/-	BHMT-04
ACE + MSF Nucleotide	ALL	BASIC ACE SUPPORT FOR ALL				
Adenosyl B12	+/-	ACAT 1-02	+/-	MTHFR 3	+/+	MTRR A66G
Adrenal Concentrate (Formerly Ora-Adrenal-80)	ALL	TOP STEP ONE/ Nutritional Groundwork	ALL	BASIC ACE SUPPORT FOR ALL	+/-	MTRR-11
AHCY/SHMT Cap	+/+	SHMT C1420T				
All in One Multi-vitamin	ALL	TOP STEP ONE/ Nutritional Groundwork	ALL	Before adding EXTRA B12 check Lithium	ALL	**BASIC METHYLATION CYCLE SUPPORT:** In order listed
	ALL	BASIC ACE SUPPORT FOR ALL	FF	VDR Fok	+/-	ACAT 1-02
	+/-	MTHFR 3	+/+	MTHFR A1298C	+/+	MTRR A66G
	+/-	MTRR-11	+/-	BHMT-02	+/-	BHMT-04
	+/+	BHMT-08	+/-	CBS C699T	+/-	CBS A360A
	+/+	SHMT C1420T	--/+-	COMT V158M (COMT H62H) -- VDR Taq Tt		
AminoAssist Cap	+/-	MTRR-11				
AminoAssist Spray	+/-	MTRR-11				
B12 Methyl Chewable	--/+-	COMT V158M (COMT H62H) -- VDR Taq Tt				

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Supplement		Supports				
B12 Chewable tablets (mix of hydroxyl, methyl, adenosyl depend on Comt/taq status)	+/-	MTHFR 3	+/+	MTRR A66G		
B12 gum (if able to chew gum)	+/-	MTHFR 3	+/+	MTRR A66G		
B12 Hydroxy Chewable	+/+	BHMT-08	--/+-	COMT V158M (COMT H62H) -- VDR Taq Tt		
B12 injections (choice of Hydroxy or Methyl depends on COMT/Taq status)	+/-	MTHFR 3	+/+	MTRR A66G		
B12 Multiple routes/ forms, support gradually increasing doses over time	+/-	MTHFR 3	+/+	MTRR A66G		
B12 patch	+/-	MTHFR 3	+/+	MTRR A66G		
BASIC METHYLATION CYCLE SUPPORT LIST	ALL	BASIC ACE SUPPORT FOR ALL	FF	VDR Fok	+/-	ACAT 1-02
	+/-	MTHFR 3	+/+	MTHFR A1298C	+/+	MTRR A66G
	+/-	MTRR-11	+/-	BHMT-02	+/-	BHMT-04
	+/+	BHMT-08	+/-	CBS C699T	+/-	CBS A360A
	+/+	SHMT C1420T	--/+-	COMT V158M (COMT H62H) -- VDR Taq Tt		
BeCalm Spray	ALL	TOP STEP ONE/ Nutritional Groundwork	ALL	Glutamate/Gaba Balance (see Companion Guide Page 20)	ALL	Before adding EXTRA B12 check Lithium
	ALL	**BASIC METHYLATION CYCLE SUPPORT:** In order listed	--/+-	COMT V158M (COMT H62H) -- VDR Taq Tt		
BHMT 1, 2, 4 + MSF Nucleotide	+/-	BHMT-02	+/-	BHMT-04		
BHMT 8 + MSF Nucleotide	+/+	BHMT-08				

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Supplement		Supports		
Bile Acid Factors	+/-	ACAT 1-02		
BioNativus Trace Minerals	ALL	TOP STEP ONE/ Nutritional Groundwork		
Biotin & Adenosyl B12	+/-	ACAT 1-02		
Black Bear Energy Drink	ALL	**BASIC METHYLATION CYCLE SUPPORT:** In order listed		
Black Bear Energy Spray or Molybdenum caps	+/-	CBS C699T	+/-	CBS A360A
Bowel Support Nucleotide	ALL	TOP STEP ONE/ Nutritional Groundwork		
CBS + MSF Nucleotide and/or Ammonia Nucleotide **(before using check taurine levels on UAA)**	+/-	CBS C699T	+/-	CBS A360A
CBS/NOS/Kidney Cap	+/-	CBS C699T	+/-	CBS A360A
Cell Food	ALL	TOP STEP ONE/ Nutritional Groundwork		
Charcoal/Mag Flush (Activated Charcoal/ Magnesium Citrate flushes)	+/-	CBS C699T	+/-	CBS A360A
Chromium Picolinate	FF	VDR Fok		
Cod Liver Oil	ALL	TOP STEP ONE/ Nutritional Groundwork		
CoEnzyme Q10 Spray and/or Coenzyme Q10 Soft Gels	+/-	ACAT 1-02		
Comfort Support Nucleotide	ALL	Glutamate/Gaba Balance (see Companion Guide Page 20)		
COMT V158M -- MSF Nucleotide	--/+-	COMT V158M (COMT H62H) -- VDR Taq Tt		
Cytokine Balance Nucleotide	ALL	TOP STEP ONE/ Nutritional Groundwork		

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Condition Note:

Supplement		Supports				
DHA Neuromins	ALL	**BASIC METHYLATION CYCLE SUPPORT:** In order listed	+/-	BHMT-02	+/-	BHMT-04
	+/+	BHMT-08				
DMG	+/-	MTHFR 3	+/+	MTRR A66G	+/+	BHMT-08
Fatigue Support Nucleotide (CFS Adults)	ALL	TOP STEP ONE/ Nutritional Groundwork				
GABA	ALL	TOP STEP ONE/ Nutritional Groundwork	ALL	Glutamate/Gaba Balance (see Companion Guide Page 20)	FF	VDR Fok
General Support Nucleotide	ALL	TOP STEP ONE/ Nutritional Groundwork				
Glucose Support	FF	VDR Fok				
Grape Seed Extract	ALL	TOP STEP ONE/ Nutritional Groundwork	ALL	Glutamate/Gaba Balance (see Companion Guide Page 20)		
GSH Caps	+/-	ACAT 1-02	+/-	BHMT-02	+/-	BHMT-04
Homeopathic BH4	+/+	MTHFR A1298C				
Hydroxy B12 Mega Drops	ALL	**BASIC METHYLATION CYCLE SUPPORT:** In order listed	+/-	ACAT 1-02	+/-	MTHFR 3
	+/+	MTRR A66G	+/+	BHMT-08	+/-	CBS C699T
	+/-	CBS A360A				

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Supplement		Supports				
Hydroxy B12 Spray (GET-B12)	ALL	**BASIC METHYLATION CYCLE SUPPORT:** In order listed	+/-	ACAT 1-02	+/-	MTHFR 3
	+/+	MTRR A66G	+/+	BHMT-08	+/-	CBS C699T
	+/-	CBS A360A	--/+-	COMT V158M (COMT H62H) -- VDR Taq Tt		
If Levels are low in hair, blood or urine or excreting very high levels consider:	ALL	Before adding EXTRA B12 check Lithium				
Jujube	ALL	Glutamate/Gaba Balance (see Companion Guide Page 20)				
Kidney Support Nucleotide	ALL	**BASIC METHYLATION CYCLE SUPPORT:** In order listed	ALL	BASIC ACE SUPPORT FOR ALL		
KuShen Sophora Flavescens	ALL	Glutamate/Gaba Balance (see Companion Guide Page 20)				
L-Theanine	ALL	Glutamate/Gaba Balance (see Companion Guide Page 20)				
Lactoferrin (Depending on Iron Levels)	+/+	SHMT C1420T				
Limit Sulfur and limited B6 (or P5P)	+/-	CBS C699T	+/-	CBS A360A		
Limit Taurine	+/-	CBS C699T	+/-	CBS A360A		
Lithium Drops (work with your Doctor)	ALL	Glutamate/Gaba Balance (see Companion Guide Page 20)				
Lithium Orotate (work with your Doctor)	ALL	Glutamate/Gaba Balance (see Companion Guide Page 20)	ALL	Before adding EXTRA B12 check Lithium		
Liver Support Nucleotide	ALL	**BASIC METHYLATION CYCLE SUPPORT:** In order listed				

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Supplement		Supports
Melatonin Sleep Spray	ALL	Glutamate/Gaba Balance (see Companion Guide Page 20)
Melatonin Sleep Spray or Melatonin if needed at bedtime	--/+-	COMT V158M (COMT H62H) -- VDR Taq Tt
MetalAway Cap	+/+	MTHFR A1298C
Methyl B12 Mega Drops	--/+-	COMT V158M (COMT H62H) -- VDR Taq Tt
Methyl B12 Mega Drops (depending on Comt/taq status)	+/-	MTHFR 3 +/+ MTRR A66G
Methyl Max Compound	--/+-	COMT V158M (COMT H62H) -- VDR Taq Tt
Methylation Support Nucleotide	ALL	**BASIC METHYLATION CYCLE SUPPORT:** In order listed
MethylMate A Compound	ALL	**BASIC METHYLATION CYCLE SUPPORT:** In order listed
MethylMate B Drops	ALL	**BASIC METHYLATION CYCLE SUPPORT:** In order listed +/- MTHFR 3 +/+ MTHFR A1298C
	+/+	MTRR A66G +/+ SHMT C1420T
Mood D Nucleotide	--/+-	COMT V158M (COMT H62H) -- VDR Taq Tt
MTHFR 3 + MSF Nucleotide	+/-	MTHFR 3
MTHFR A1298C+ Liver Support Cap	ALL	TOP STEP ONE/ Nutritional Groundwork +/+ MTHFR A1298C +/+ BHMT-08
MTHFR A1298C+ MSF Nucleotide	+/+	MTHFR A1298C
MTR/MTRR + MSF Nucleotide	+/+	MTRR A66G
MTR/MTRR/SUOX Basic Methylation Support/Sulfite Ingestion Cap	+/+	MTRR A66G
MTRR11 + MSF Nucleotide	+/-	MTRR-11

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Supplement		Supports				
Nerve Calm Formula Nucleotide	ALL	TOP STEP ONE/ Nutritional Groundwork	ALL	Glutamate/Gaba Balance (see Companion Guide Page 20)		
Ora-Kidney	ALL	TOP STEP ONE/ Nutritional Groundwork				
Passion Flower (Passiflora spp. Flower & Leaf)	ALL	Glutamate/Gaba Balance (see Companion Guide Page 20)				
Phosphatidyl Serine Complex (PS/PE/PC)	ALL	**BASIC METHYLATION CYCLE SUPPORT:** In order listed	+/-	BHMT-02	+/-	BHMT-04
	+/+	BHMT-08				
Placenta	+/-	MTRR-11				
Potassium	ALL	Glutamate/Gaba Balance (see Companion Guide Page 20)				
Probiotics- several types-rotate daily	ALL	TOP STEP ONE/ Nutritional Groundwork				
Progesterone Cream (Pro-Gest Body Cream)	ALL	Glutamate/Gaba Balance (see Companion Guide Page 20)	ALL	BASIC ACE SUPPORT FOR ALL		
Pycnogenol	ALL	TOP STEP ONE/ Nutritional Groundwork	ALL	Glutamate/Gaba Balance (see Companion Guide Page 20)		
Red Rice Yeast & CoEnzyme Q10	+/-	ACAT 1-02				
Relaxation Support	ALL	Glutamate/Gaba Balance (see Companion Guide Page 20)				
Resveratrol Spray	ALL	TOP STEP ONE/ Nutritional Groundwork	ALL	Glutamate/Gaba Balance (see Companion Guide Page 20)		

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Supplement		Supports				
Riboflavin 5'-Phosphate (Low Dose ACAT/BHMT)	+/-	ACAT 1-02				
Ribose (in MitoForce, Black Bear Drink, CoEnzyme Q10)	+/-	ACAT 1-02				
Royal Jelly (Only if **NO** bee allergies)	+/+	MTHFR A1298C	+/-	MTRR-11		
Run UEE & HMT to Determine Mineral Support	ALL	TOP STEP ONE/ Nutritional Groundwork				
SAM-e (Low Dose in Methyl Max)	ALL	**BASIC METHYLATION CYCLE SUPPORT:** In order listed	+/+	BHMT-08	--/+-	COMT V158M (COMT H62H) -- VDR Taq Tt
SHMT + MSF Nucleotide	+/+	SHMT C1420T				
SHMT Spray	+/+	SHMT C1420T				
Special Digestive Enzymes	ALL	TOP STEP ONE/ Nutritional Groundwork	FF	VDR Fok	+/-	ACAT 1-02
Stress Foundation Nucleotide	ALL	TOP STEP ONE/ Nutritional Groundwork	ALL	BASIC ACE SUPPORT FOR ALL		
Taurine (not for CBS + or SUOX mutation)	ALL	Glutamate/Gaba Balance (see Companion Guide Page 20)				
UAA (Urine Amino Acids) Test	+/-	CBS C699T	+/-	CBS A360A		
Ultimate B Complex	ALL	TOP STEP ONE/ Nutritional Groundwork	+/+	SHMT C1420T		
Valerian Root	ALL	Glutamate/Gaba Balance (see Companion Guide Page 20)				

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Supplement	Supports
Vanadyl Sulfate	FF VDR Fok
VDR Fok + MSF Nucleotide	FF VDR Fok
VDR Fok/Pancreatic Cap	ALL TOP STEP ONE/ Nutritional Groundwork FF VDR Fok
VDR Taq + MSF Nucleotide	--/+- COMT V158M (COMT H62H) -- VDR Taq Tt
Vita D-Light Spray or Vitamin D	ALL TOP STEP ONE/ Nutritional Groundwork FF VDR Fok --/+- COMT V158M (COMT H62H) -- VDR Taq Tt
Vitamin C	ALL TOP STEP ONE/ Nutritional Groundwork
Vitamin K (Super K) (In VDR, ACAT, Mitoforce)	ALL TOP STEP ONE/ Nutritional Groundwork
VitaOrgan	ALL TOP STEP ONE/ Nutritional Groundwork ALL **BASIC METHYLATION CYCLE SUPPORT:** In order listed +/- ACAT 1-02 +/- MTRR-11 +/- BHMT-02 +/- BHMT-04
Watch Chromium & Vanadium levels on UEE	FF VDR Fok
Zen	ALL Glutamate/Gaba Balance (see Companion Guide Page 20)
Zinc Lozenges	ALL TOP STEP ONE/ Nutritional Groundwork

Why You Should Care About Methylation

The Methylation Cycle is the intersection of several important pathways in the body; the common point is the need for methyl groups. Recall that methyl groups are simply small chemical compounds whose structure is similar to water. The ability to generate and move these groups is critical to health; these groups are needed for a large number of reactions in the body. *"Methylation takes place over a billion times a second in the body. It is like one big dance, with biochemicals passing methyl groups from one partner to another"* (The H Factor, Dr.James Brady and Patrick Holford).

The role of the methylation cycle in your body

The methylation cycle is the ideal pathway to focus on for nutritional genetic analysis because the places where mutations occur is well defined and it is clear where supplements can be added to bypass these mutations. In addition to its editing role, the function of this pathway is essential for a number of critical reactions in the body. One consequence of genetic weaknesses (mutations) in this pathway is increased risk factors for a number of serious health conditions. Defects in methylation lay the appropriate groundwork for the further assault of environmental and infectious agents resulting in a wide range of conditions including diabetes, cardiovascular disease, thyroid dysfunction, neurological inflammation, chronic viral infection, neurotransmitter imbalances, atherosclerosis, cancer, aging, schizophrenia, decreased repair of tissue damage, improper immune function, neural tube defects, Down's syndrome, Multiple Sclerosis, Huntington's disease, Parkinson's disease, Alzheimer's disease, and autism.

- **Inflammation, bacterial, and viral infection**

When you have bacterial or viral infections in your system it increases the level of inflammation in your body. Chronic inflammation can therefore exacerbate existing genetic mutations in this same pathway. The inability to progress normally through the methylation pathway as a result of methylation cycle mutations combined with the impact of viral and bacterial infections can further compromise the function of this critical system in the body.

- **New cells and the immune system**

The building blocks for DNA and RNA require the methylation pathway to function optimally. Without adequate DNA and RNA it is difficult for the body to synthesize new cells. New cell synthesis is needed to repair damaged cells, to maintain the lining of the gut, to make new blood cells as well as for your immune system that defends you against infection.

T cells are a key aspect of your immune system and they require new DNA in order to respond to foreign invaders. T cell synthesis is necessary to respond to bacterial, parasitic and viral infection, as well as for other aspects of the proper functioning of the immune system.

- **Herpes, hepatitis and other viruses**

In addition, decreased levels of methylation can result in improper DNA regulation. DNA methylation is necessary to prevent the expression of viral genes that have been inserted into the body's DNA. Loss of methylation can lead to the expression of inserted viral genes such as herpes and hepatitis among other viruses.

- **Sensory Overload**

Proper levels of methylation are also directly related to the body's ability to both myelinate nerves and to prune nerves. Myelin is a sheath that wraps around the nerve to insulate and facilitate proper nerve reaction. Without adequate methylation, the nerves cannot myelinate in the first place, or cannot remyelinate after insults such as viral infection or heavy metal toxicity. A secondary effect of a lack of methylation and hence decreased myelination is inadequate pruning of nerves. Pruning helps to prevent excessive wiring of unused neural connections and reduces the synaptic density. Without adequate pruning the brain cell connections are misdirected and proliferate into dense, bunched thickets. When nerves grow in this unregulated fashion it can cause confusion processing signals. Synesthesia occurs when the stimulation of one sense causes the involuntary reaction of other senses, basically sensory overload.

- **Serotonin, dopamine and ADD/ADHD**

Methylation is also directly related to substances in your body that affect your mood and neurotransmitter levels of both serotonin and dopamine. In addition to its direct role as a neurotransmitter, dopamine is involved in assuring your cell membranes are fluid and have mobility. This methylation of phospholipids in the cell membranes has been related to ADD/ADHD. Membrane fluidity is also important for a variety of functions including proper signaling of the immune system as well as protecting nerves from damage. A number of serious neurological conditions cite reduced membrane fluidity as part of the disease process including MS, ALS, and Alzheimer's disease. In addition, phospholipid methylation may be involved in modulation of NMDA (glutamate) receptors, acting to control excitotoxin damage.

Methylation as one piece of a more complex puzzle

In general, single mutations or *biomarkers* are generally perceived as indicators for specific health issues. However, it is possible that for a number of health conditions, it may be necessary to look at the entire methylation pathway as a biomarker for underlying genetic susceptibility for non-ideal health. It may require expanding the view of a biomarker beyond the restriction of a mutation in a single gene to a mutation somewhere in an entire pathway of interconnected function. For more information go to www.feelgoodbiochem.com.

This does not mean that every individual with mutations in this pathway will have one of the health conditions listed above. It may be a necessary but not a sufficient condition. Most health conditions in society today are multifactorial in nature. There are genetic components, infectious components and environmental components. A certain threshold or body burden needs to be met for each of these factors in order for multifactorial disease to occur. However, part of what makes the methylation cycle so unique and so critical for our health is that mutations in this pathway have the capability to impair all three of these factors. This would suggest that if an individual has enough mutations or weaknesses in this pathway, it may be sufficient to cause multifactorial health issues. Methylation cycle mutations can lead to chronic infections, increased environmental toxin burdens and have secondary effects on genetic expression.

Again, nutrigenomic test results should help to put your mind at ease by giving you suggestions that you can act on. Nutrigenomics is a form of genetic testing that supplies information that can translate into positive constructive action. Dr. Yasko sees the ultimate goal of nutrigenomic testing to serve as a guide toward proper supplementation to bypass genetic weaknesses identified by SNP results.

Different Methodologies for Nutrigenomic Testing

There are discrete reasons why Dr. Yasko chooses to use blood spot samples and the MassArray technology to screen for these SNPs rather than using saliva samples and BeadChip technology. This is not to minimize the value of the BeadChip technology. It is a wonderful tool for what it was designed for, to screen a large number of genes in a rapid time frame. This is great if you are looking for a broad picture and not certain which SNPs in particular you are most concerned with. However, given the fact that we know the SNPs we are interested in looking at, from Dr. Amy s vantage point it makes more sense to use a technique designed to do just that.

In fact, in a number of research situations the BeadChip technology is initially used to narrow down which SNPs are of interest and then use the MassArray technique to more critically study those SNPs of interest *(Mol Ecol.Suppl 1:132-46 2010 Mar;19 and Genet 2008 4(4))*. The bottom line is to pick the right tool to do the job that you are looking to accomplish. *"Different technologies are appropriate for different types of projects and scales of SNPs to be genotyped"*. *(http://cshprotocols.cshlp.org/content/2009/11/pdb.top62/F1.expansion.html).*

There are several major differences between the test Dr. Yasko prefers and other tests that are available. One point of difference is in terms of the technology used to analyze the samples and another is the sample quality itself. Dr. Amy is more comfortable with the results obtained using the Mass Array TaqMan technology. According to the literature, MassArray technology is greater than 99% reliable and in some cases has been reported to be 100% accurate in looking at SNPs. *"Given sufficient DNA concentration and quality, the designed iPLEX/TaqMan test had an accuracy of 100% for the designed assays. These results suggest that the combined iPLEX/TaqMan test is an outstanding tool for identification of recurrent mutations" (Combined iPLEX and TaqMan Assays to Screen for 45 Common Mutations in Lynch Syndrome and FAP Patients J Mol Diagn. 2010 January; 12(1): 82 90).* BeadChip technology, is a faster, less expensive method that can look at a larger number of SNPs at one time, but with a potentially lower sensitivity depending on the way in which sample bias is corrected for. *"In the interests of practicalities and cost, these results suggest that single samples can generate reliable data, but only after careful compensation for technical bias in the experiment. We recommend that investigators appreciate the propensity for such variation and that the use of suitable correction methods become routine during the statistical analysis of the data." (Correcting for intraexperiment variation in Illumina BeadChip data is necessary to generate robust gene-expression profiles. BMC Genomics 2010 11:134.)* Thus, while the level of sensitivity may be as high as 94%, for any given sample on any given SNP for any given individual it may also be as low as 75%.

To put this in less technical terms, go back to the concept of thinking of SNPs like accidents on a highway. These accidents on the highway of the methylation cycle cause issues in the traffic flow along those highways, necessitating that you take a detour to get around the traffic accident. So, working with that analogy think of BeadChip as a traffic helicopter that flies high up above the highway to look to see where there may be issues on the road. This helicopter is responsible for a very large area (ie the entire state of Maine) and so it is flying quickly to cover a large region. It is able to detect areas where traffic is stopped but may not be able to discern between a minor fender bender, a serious fatal accident or a car stopped by the side of the road to ask for directions or one whose radiator has overheated.

In order to get more specific details of what has caused the traffic delay the helicopter can call in local police to have actual 'feet on the ground' to assess the situation more closely. Compare this to MassArray, where we know the actual locations we are interested in. We know the exact intersection/cross streets where we want to know if there is a traffic issue or not. So ahead of time we have 'eyes on the ground' placed at those precise 30 intersections looking to see if there is an issue or not. Clearly both techniques have value but in our situation, where we know which SNPs we are most interested in the greater accuracy and sensitivity of having eyes on our 30 specific intersections ahead of time makes the most sense for the Yasko protocol.

The second area of difference between BeadChip and MassArray options is the sample type itself. The BeadChip is using saliva and the MassArray test for the methylation SNPs (or blood draws from your doctor and sent to a test lab that does SNP testing) use blood samples. Initially we used saliva samples for testing. Dr. Yasko became concerned that saliva could give false positive/negative results in spite of the sophisticated Mass Array technology that was being utilized to identify SNPs within the samples. There are internal checks and balances in the SNP panel and we were finding that many of the saliva samples had to be rerun multiple times or even new samples submitted to reduce questionable results. The samples were rerun until it was felt that all SNPs were evaluated accurately but this caused time delays and in some cases multiple sample collections and reruns. The lab was able to design a simple blood spot method to have the ability to limit the potential issues with some saliva samples while maintaining the convenience of in home testing. Studies by other researchers comparing the use of saliva versus blood for SNP testing have found that saliva yields results 89% versus blood at 99% results. *(Hu Y, Ehli EA, Nelson K, Bohlen K, Lynch C, et al. (2012) Genotyping Performance between Saliva and Blood-Derived Genomic DNAs on the DMET Array: A Comparison. PLoS ONE 7(3): e33968. doi:10.1371/journal.pone.0033968)*. To expand upon the traffic helicopter analogy, using saliva samples may be creating fog so that it is more difficult for that helicopter to see what is going on. Thus the combination of the lack of eyes on the ground at specific intersections and the potential for fog may make that technology less applicable to a nutrigenomic situation where we know exactly which specific intersections we are interested in.

The third area of difference is in what the test is trying to accomplish. As alluded to above, the BeadChip technology is designed to give you an overview of a large number of genes that may or may not be in the same pathway. The Mass Array SNP test is looking at specific, well defined genes in a very particular pathway. So, 30 very specific genes in a pathway that is critical for health as opposed to a much larger and broader overview. To expand upon the difference between this test and others is to think of it in terms of a road map.

If you wanted to travel from your hometown to Bethel, Maine you would need a map with detailed directions. This would be especially important if certain roads along the way were closed due to construction, bridges out because of flooding, or other road detours. It would help to have a detailed map drawn for you that took all of these specific situations into account. Your nutrigenomic test tells you where the "construction" sites are located, which bridges are out and where detours are on your individualized map. With this knowledge you can put together an analysis that will help you to get from your hometown to Bethel, Maine without getting stuck in a ditch or lost on a detour. The more information you have about specific genes in this particular pathway the easier it is to construct your personal map. This is analogous to having the model of your car, knowing how many miles per gallon you get, how often you feel you need to stop at a rest area and when you need to fill your tank or take a break from driving. With this information you are in a better position As always work with and defer to your doctor to plan your trip. This is different from other tests that may tell you where your hometown is located and your destination lies on a map, but without any of the specific information between those two points. Without the details, you do not know if the route you may choose has been closed, if the bridge is out, of if there is a detour that will add more time to your travel. Given only a starting and stopping point, or even if you are just missing ***a few key points*** on the map means the rest of the trip may simply be guesswork. The nutrigenomic test that Dr. Yasko prefers is designed to take the guesswork out of your trip to health and wellness. Compared to other tests that look at isolated genes in a wide range of pathways, focusing on the methylation cycle allows you to look comprehensively at a very critical pathway in the body and from that construct a personal road map to health and wellness.

There is one final **critical point** that needs to be reiterated with respect to SNP testing. There are approximately 25,000 genes in the human genome. Dr. Yasko personally believes in only looking at SNPs that are in well-defined pathways where it is clear how to add nutritional support to bypass imbalances. Having a laundry list of SNPs without a way to use nutritional support is not consistent with the way she approaches health. So, whether you have a test that gives you 1000 or 5000 SNPs this is still only a fraction of the total number of genes in your body and frankly having more SNPs is not the issue. The real question is whether the SNPs you have are in a pathway that has been characterized so you know what to do to help restore your body to health. The reason Dr. Yasko focuses on the methylation cycle is that it is a well-defined pathway, it is very clear where nutritional support can bypass mutations and the pathway we look at IS the system the body uses to edit and correct problems with other genes. So regardless of how many other SNPs there are in the 25,000 or so other genes in the body, IF those genes are regulated by methylation, then having your methylation cycle in balance gives you the tools you need to help to turn on or off those other genes that are NOT part of the 30 SNP methylation panel. This is called ***epigenetics***, and Dr. Yasko has given entire talks just on this topic. Having the methylation cycle function optimally and bypassing SNPs in this pathway allows the global editing function in your body to help to correct issues with any number of other genes in the system. THIS is why this pathway is so critical for health and wellness.

Dr. Amy Yasko
Ph.D, NHD, AMD, FAAIM, HHP, CTN

REMEMBER your DNA does not change. This is a test that you will run ONCE in your lifetime. Unlike the follow up biochemical testing that you run routinely to check that the supplementation you are using is actually making a difference, a nutrigenomic test focusing on the methylation cycle is something you will run only one time. You will work with your doctor to determine supplementation based on these SNPs for the rest of your life.

Additional Scientific Background and further testing

As already explained your DNA will not change so once you have nutrigenomic test results those will not change over your lifetime.

Unlike genetic tests, biochemical tests will change over time. Biochemical testing measures the amount or activity of a particular enzyme or protein from a sample of urine or stool or hair. Biochemical testing can be used to assess the effect of supplementation on your system. Ideally, the goal is to use the knowledge of your genetics to make informed decisions on how to supplement and bypass weaknesses in your system. Then use regular biochemical testing to monitor the progress of your supplementation to bypass mutations. For more information go to www.feelgoodbiochem.com.

For current information, updates and findings please join the discussion group at www.ch3nutrigenomics.com.

Dr. Amy Yasko
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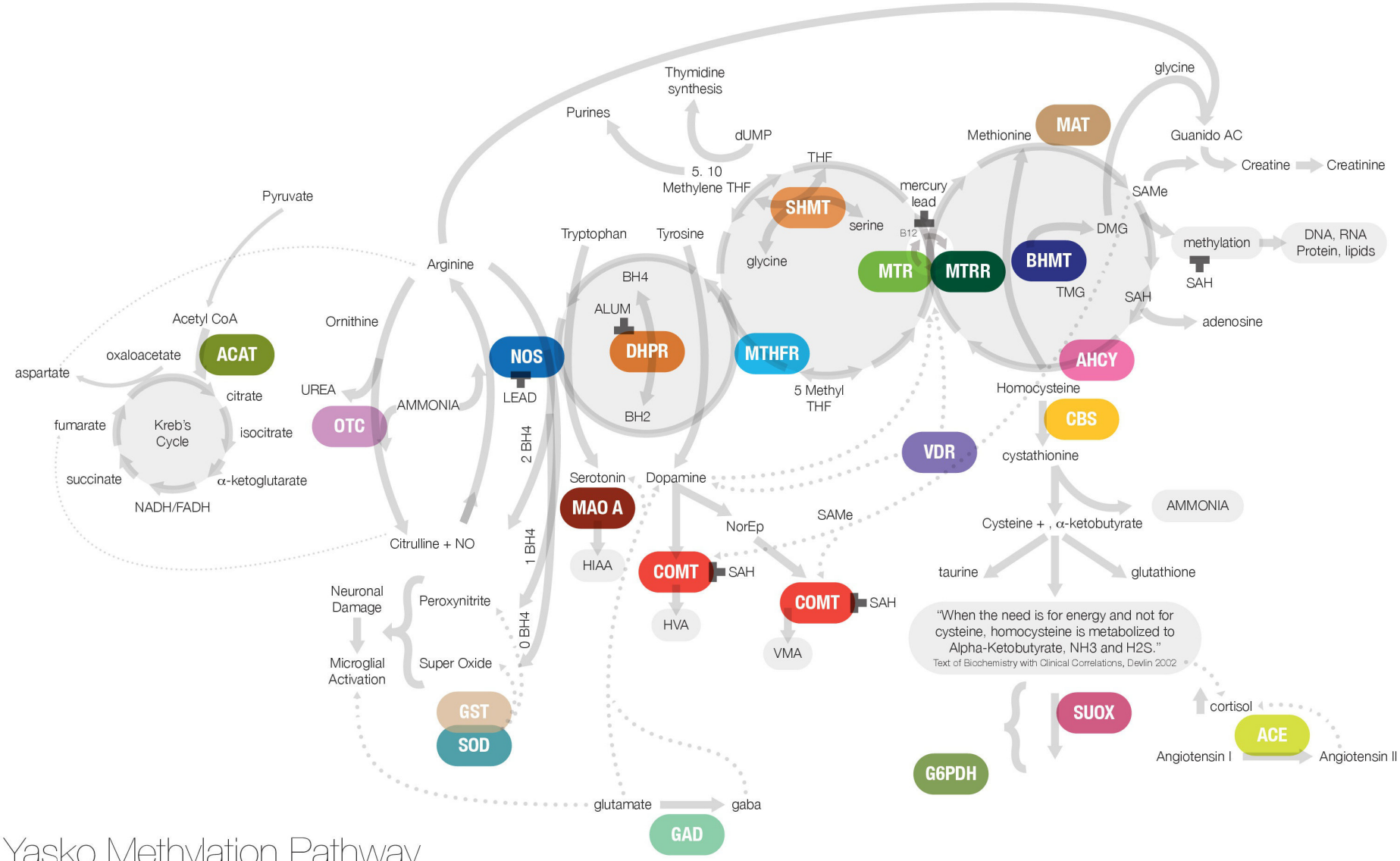

Yasko Methylation Pathway

Dr. Amy Yasko
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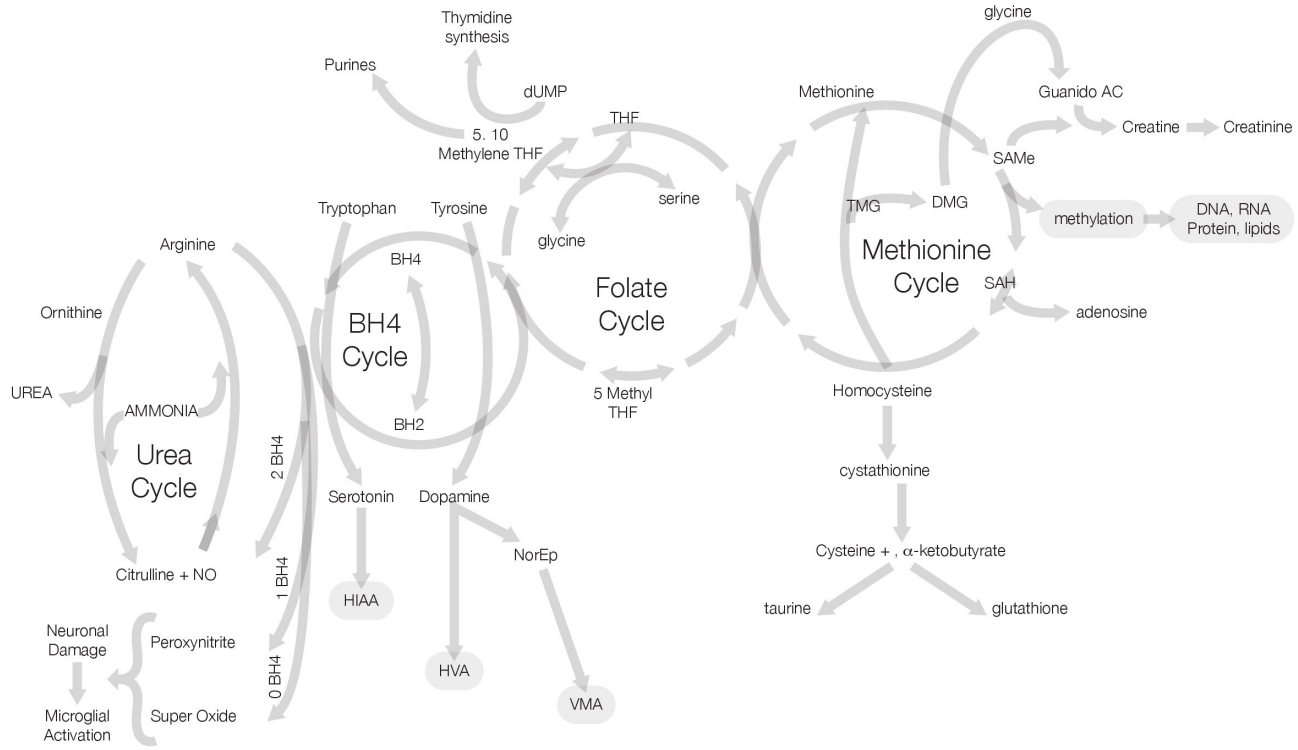
Yasko Methylation Pathway

1 The four cycles that make up the Methylation Cycle. This first diagram shows the pathways and the biochemical compounds that are a part of these cycles.



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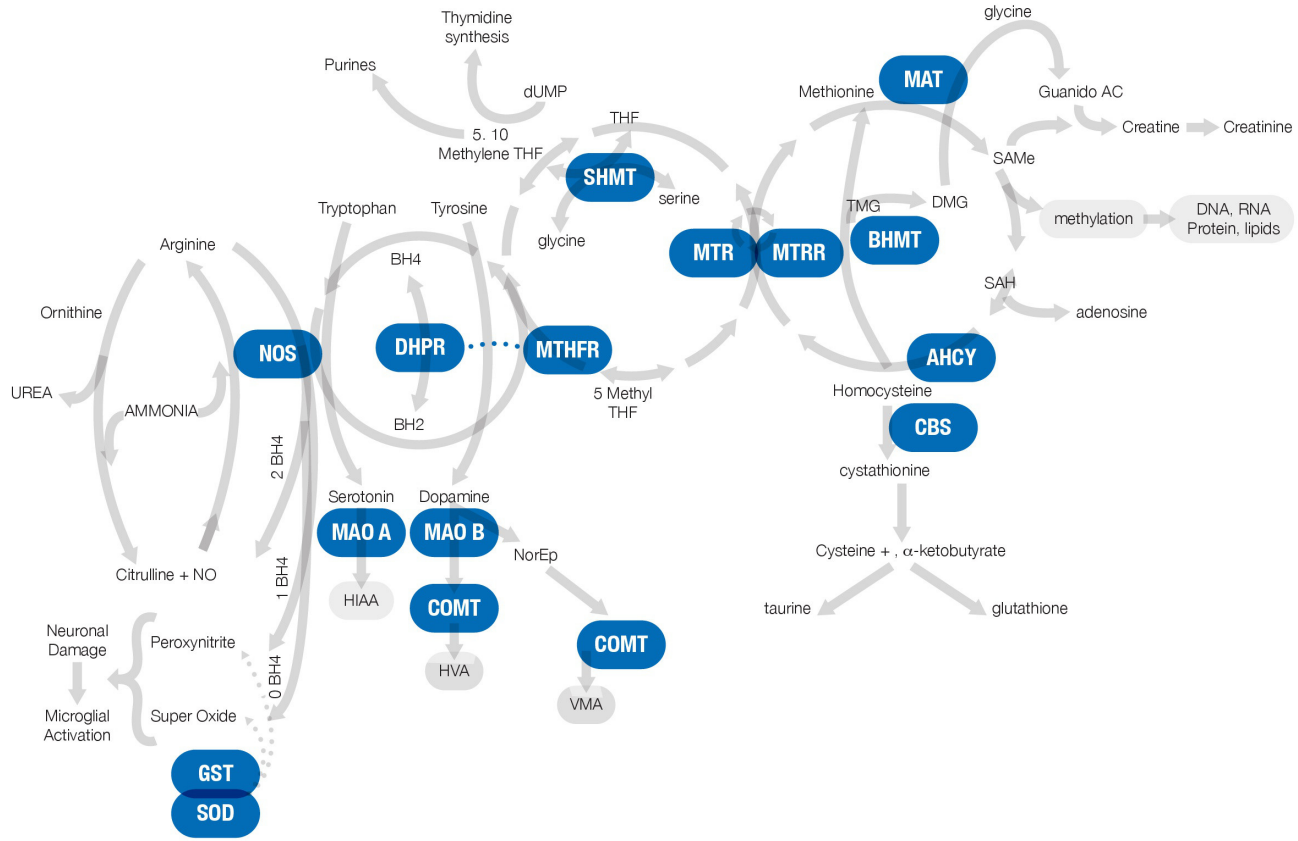

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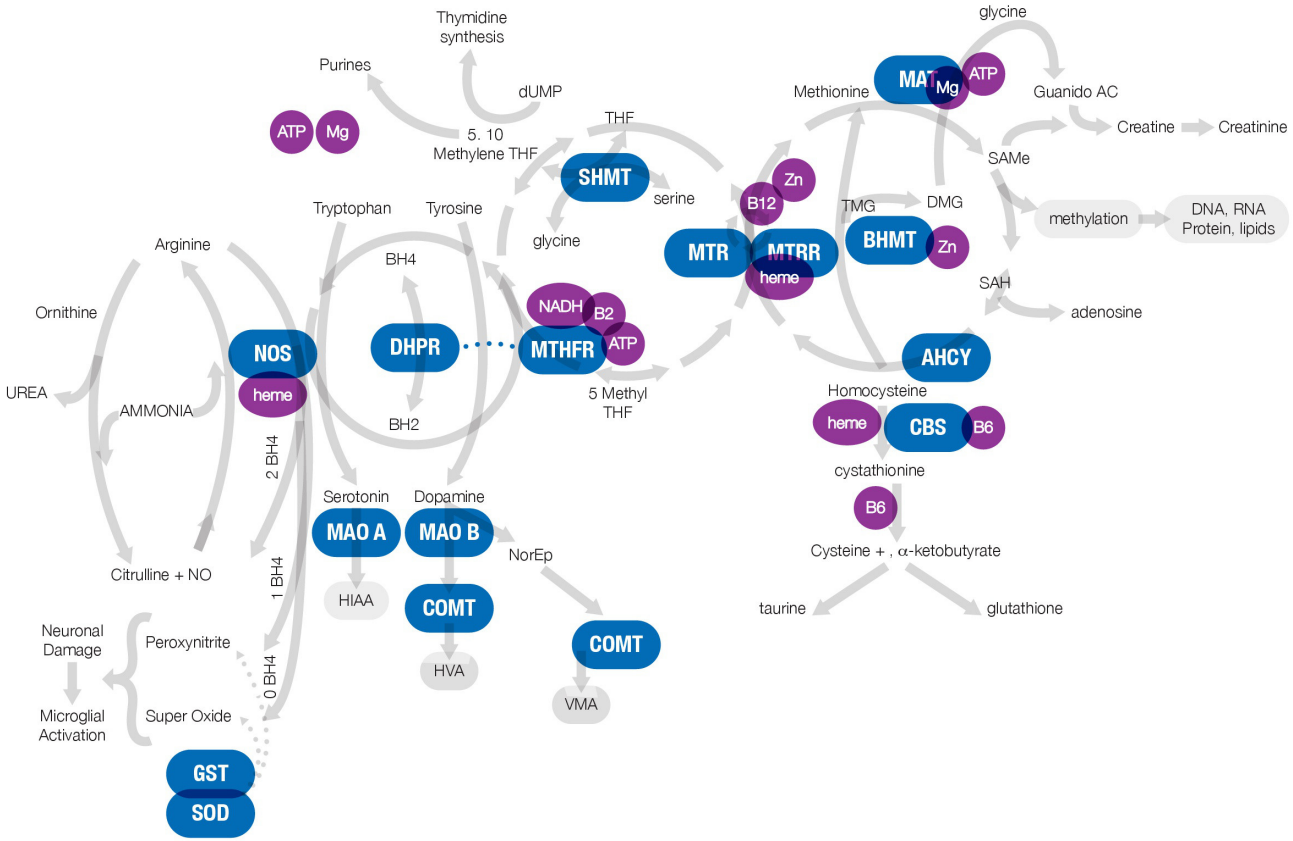

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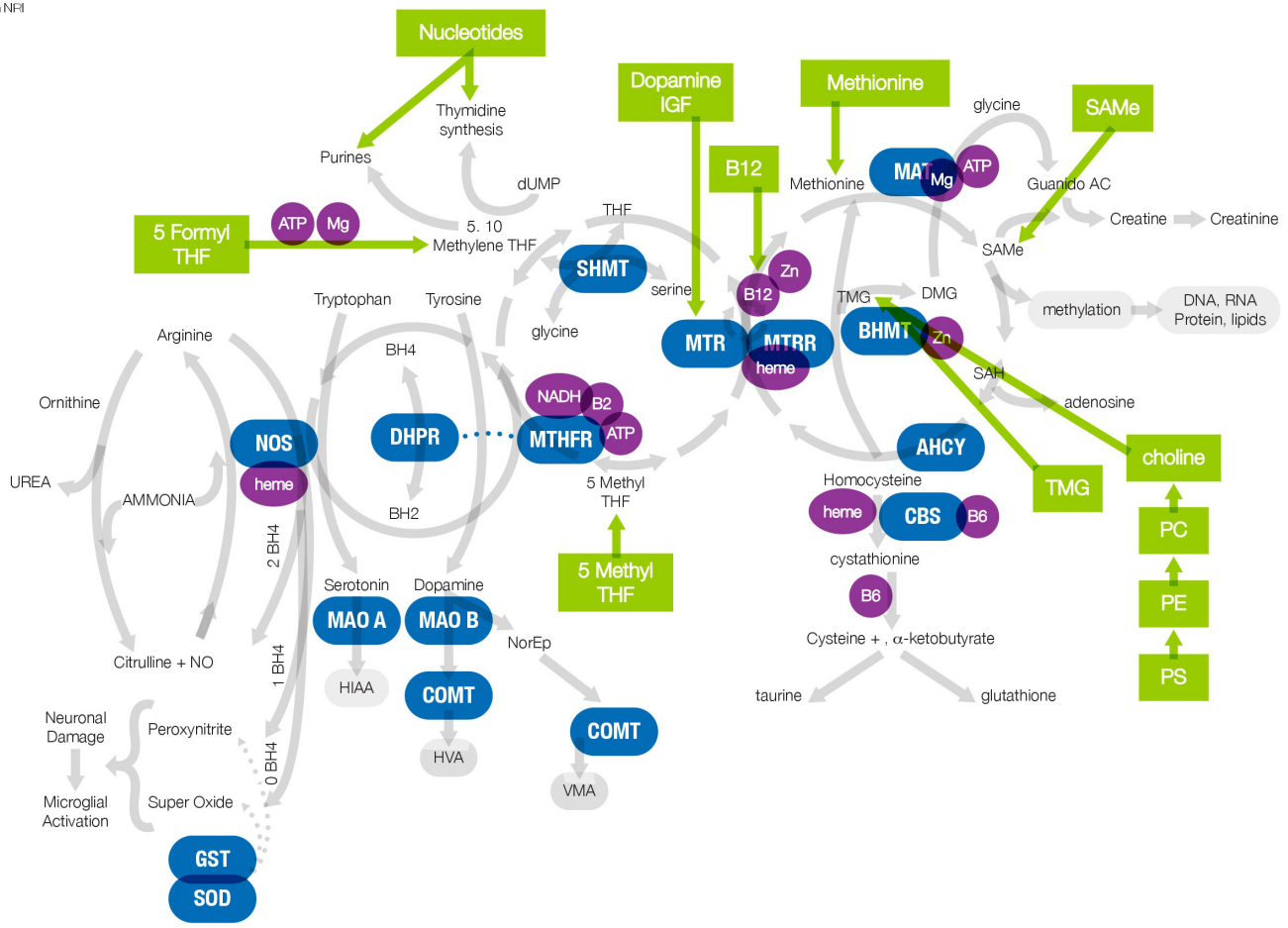

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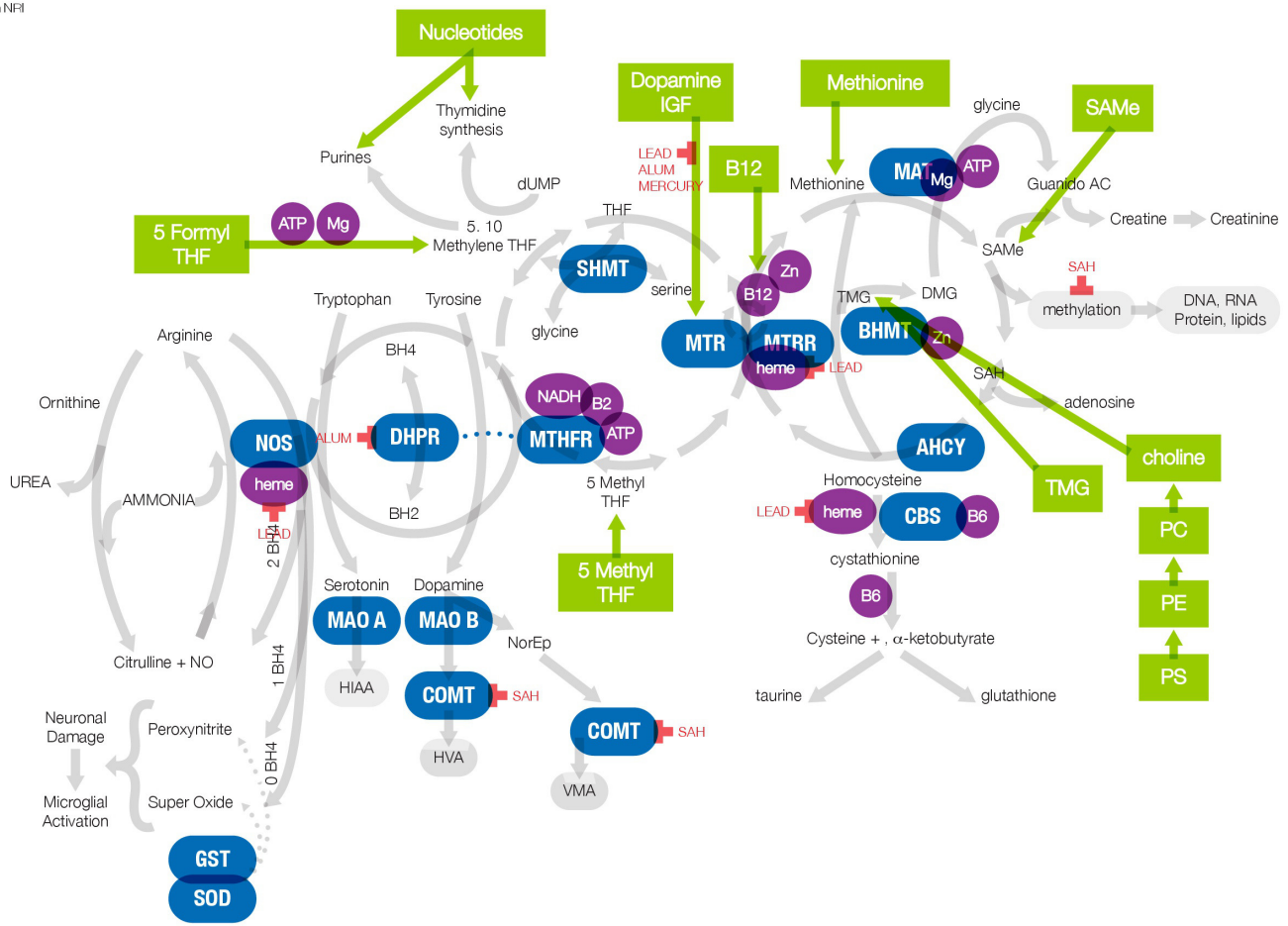

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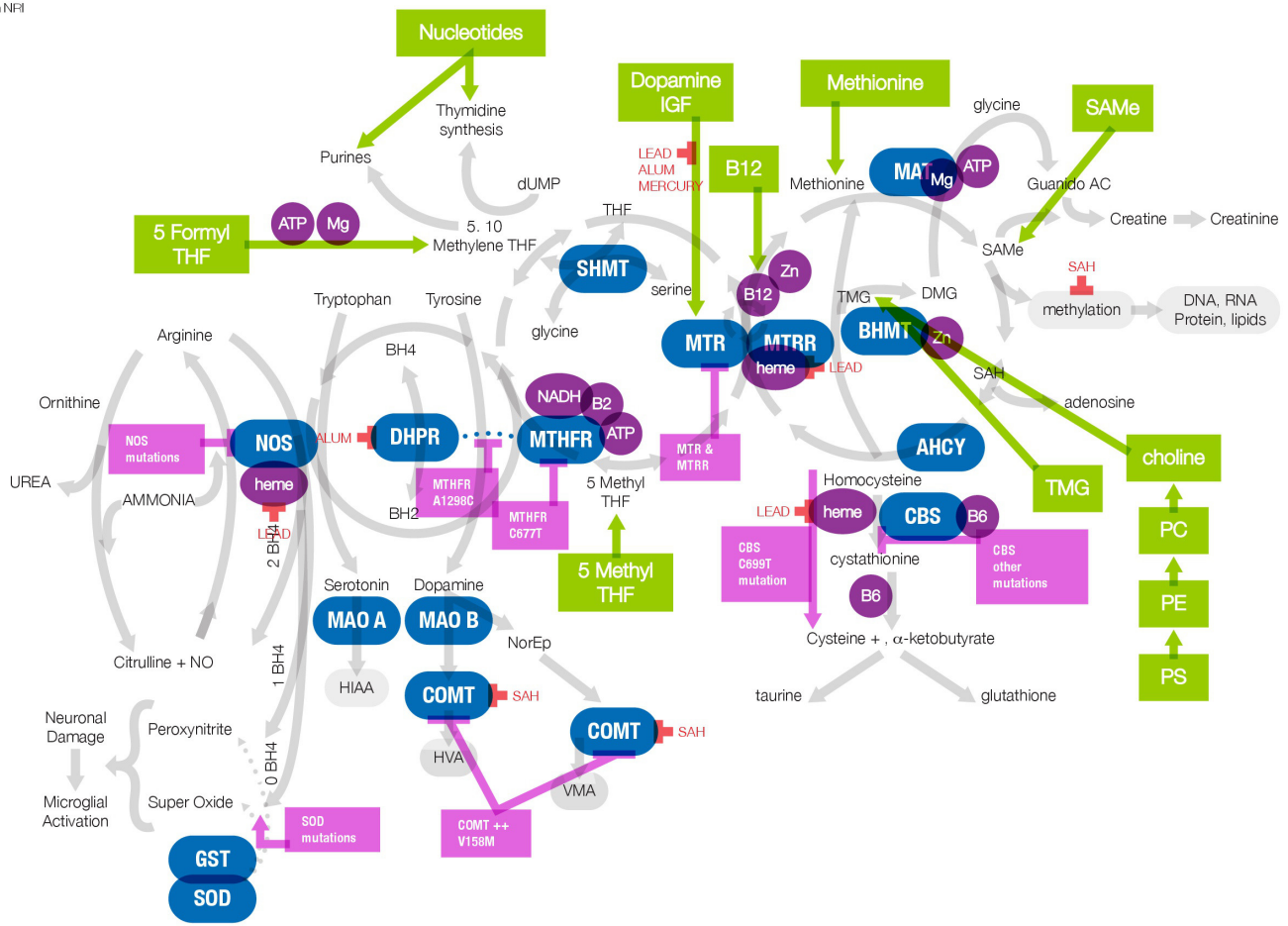
6 The actual SNPs, or mutations in the genes are noted in pink. Recall that the genes in this pathway that are looked at by nutrigenomic testing are in blue boxes. The pink boxes show where the mutations in these genes occur thus affecting the position in the cycle where they are located.



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