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

General Important Information to Guide You on Your Road to Wellness

This document is a tool to help you to understand **"the why"** behind the supplements, herbs and vitamins that were suggested in your MPA to help to bypass weaknesses in a particular nutritional pathway in your body. As discussed below this analysis focuses on the methylation pathway. What I call the "methylation pathway" for the purpose of this document, the MPA and in the Genetic Bypass book is the intersection of several biochemical pathways such that the common point is a need for methyl groups. There are a number of other nutrigenomic tests available. What is special about this test and analysis is that it comprehensively looks at one pathway. One way to think about the difference between this analysis, and others is to think about it in terms of a road map. If you wanted to travel from your hometown to my 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, and 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 me where the "construction" sites are located, where detours are, and which bridges are out on your individual map. With this knowledge I can put together an analysis that will help you to get from your hometown to my hometown without getting stuck in a ditch or lost in a detour. The more information I have from your file the easier it is for me to construct your map. This is analogous to giving me the model of your car, 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 the tank or take a driving break. With this information I am in a better position to put the details into your trip. This is different from other tests that may tell you where your hometown and destination are on the map, but without any of the detailed information between the two points. Without the details you do not know if the route you may choose 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 that you have taken and the MPA and this document are designed to take the guesswork out of your trip to health and wellness.

Just as the physical location of your hometown and my hometown will not change on the map, your genetics also will not change over time. For this reason the information you have received will serve as a roadmap for the future. Suggestions that are made may be valid today, as well as next week, next year or ten years from now. For this reason I have tried to cover any contingencies that you may need to deal with in the future. Going back to the roadmap analogy, if I know that work is planned on a road for a major reconstruction next spring, I have taken that into account when supply you with information. As a result the MPA will list a large number of supplements that you may not need to use at this time, but need to know about should instances arise in the future that require their use.

This gets me to my next point, which is that unlike the MPA this document does not contain a laundry list of supplements that you need to buy. Instead it explains the rationale behind supplements that are suggested and requires that you choose from those that are listed. Again, if you think about the road map that I am drawing for you, it is as if I have given you several different routes to get from your hometown to my hometown. You have the ability to choose which road you may want to take today, which may be a slightly different route than you would take a year from now.

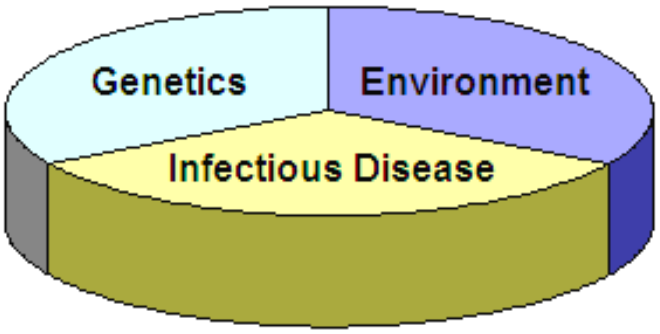
This approach also requires that you really understand the process so that you are in a position to make an informed choice. This means that you may need to read this document several times before you are ready to choose your supplements from the lists included in your this document and your MPA and begin your "trip". The protocol I use is not a quick fix, it is truly a program that requires a commitment to immerse yourself in it, understand it, and embrace it.
Read it, learn it, live it…

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

- **Nutrigenomic Emphasis on the Methylation Cycle**

The methylation cycle is the ideal pathway to focus on for nutrigenomic analysis and supplementation. The function of this pathway is essential for a number of critical reactions in the body. Consequences of genetic weaknesses (mutations) in this pathway are increased risk factors leading to a number of serious health conditions. Defects in methylation cycle lays 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, diabetes, 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, as well as autism.

In general, single biomarkers are identified as indicators for specific disease states. However, it is possible that for a number of health conditions, including autism, it may be necessary to look at the entire methylation pathway as "a biomarker" for underlying genetic susceptibility for a disease state. 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.



This does not mean that every individual with mutations in this pathway will be autistic or 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. While the relative contribution of each of these components may differ from one individual to the next, each of these components does play a role for all of us. 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 mutlifactorial disease, as methylation cycle mutations can lead to chronic infectious diseases, increased environmental toxin burdens and have secondary effects on genetic expression.

In addition, the methylation cycle can affect both "nature" as well as "nurture" by virtue of the fact that methylation cycle mutations have primary effects on genetics as well as on epigenetics. The initial methylation cycle mutations themselves play a role, just as any mutations would. In addition, methyl groups help to turn on and off sections of DNA in our bodies, so there is a secondary impact of these mutations on the body. One analogy that I often use to describe this is to think about our DNA like a charm bracelet. Mutations in the basic DNA are like breaks in the links of the bracelet. We also have charms on this bracelet. The secondary effect of lacking methyl groups is that the charms are also broken. If we were to have mutations elsewhere in the body we might still have broken links in our bracelet, but the charms, if they were intact would help to hold the links of the bracelet together. Another way to illustrate the difference between "genetics" and "epigenetics" is to think about the following...suppose that your computer has a broken "M" key, so that when you go to type a document the letter "M" will always be missing from the words that include "M" . This would be analogous to the mutations that we look at. It is like having a broken letter "M" and so that will not change over time. This is part of the reason that the nutrigenomic profile is so useful is that the information you get today, will also be applicable 5 years from now, 10 years from now, 50 years from now. So, your actual genetics and mutations will not change, just as the broken "M" will not magically fix itself. On the other hand, when you type a document your computer also has an edit or word processing functions, so that if you typed "_iss" your computer might say...did you mean "miss"?? In this way the editing function will catch the mistakes that occur because of the broken "M" key. While you still will not be able to type a letter "M" , you will be able to spell the words correctly in your document because the editing function will find the mistakes and point them out to you so that all you need to do is click on the correct spelling which gets around the broken "M" key. ***Now*** the editing function on your computer is analogous to epigenetics in this example. Which can change over time and it is also inherited. While your actual DNA does not change, the way in which it is "edited" can change over time. However, this is where we get into the catch 22...the editing function relies on methylation. The way that the editing works is to add methyl groups to the DNA to turn on and off certain areas. SO...while mutations in other areas would be less of an issue, the mutations that we look at, in the methylation cycle are of such central importance as they affect the actual

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

DNA sequence, as well as the editing function. While the actual mutations will not change with methylation cycle support, the editing function should be able to change over time.

Also, remember that I feel that autism is a multifactorial condition. It is the metals, infectious agents, vaccines etc against a background of underlying genetic susceptibility that can create the condition. We can find individuals who have similar genetics but are not autistic perhaps because they were not exposed to the same metals or infectious agents that tipped the scales toward autism in spite of their genetics. However, where this pathway is so central to health and is needed for the body's editing function, you can see why I think it is so important to look at all of our nutrigenomic weaknesses and supplement to bypass mutations and restore and optimize the editing function even if we are not concerned about autism. I think this is why we are finding that more and more adults are joining out discussion group because what I am trying to do here is more universal in terms of helping to support the body for optimal function of this critical pathway.

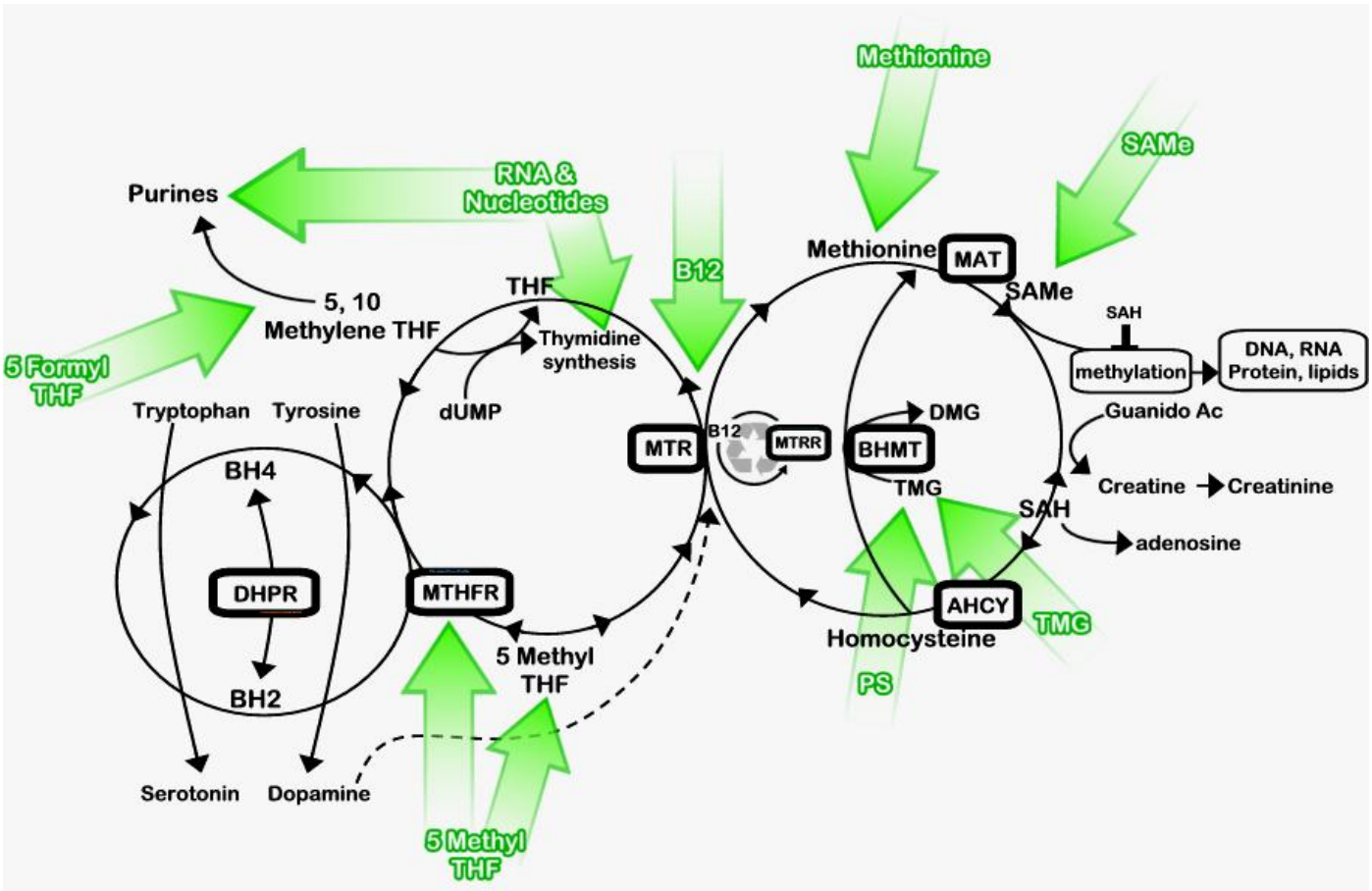
.

Because methylation is so central, it is important to try to supplement the body with the appropriate nutrients to bypass these mutations. It is similar to finding out that you have diabetes. While this is a genetic mutation, once you understand where the problem occurs, you can look to bypass it through the use of insulin. Even if you need to use insulin for a lifetime, with knowledge you have the ability to know what you need to do to support the weaknesses in the body. Folates are essentially chains of glutamate. If a form of folate is used that the body cannot process it can be broken down into glutamate molecules. For this reason high doses of folate supplements that do not take nutrigenomics into consideration may cause increases in glutamate. This is just one example of why it is important to supplement this cycle properly based on a knowledge of methylation cycle nutrigenomics.

- **Methylation Cycle Basics**

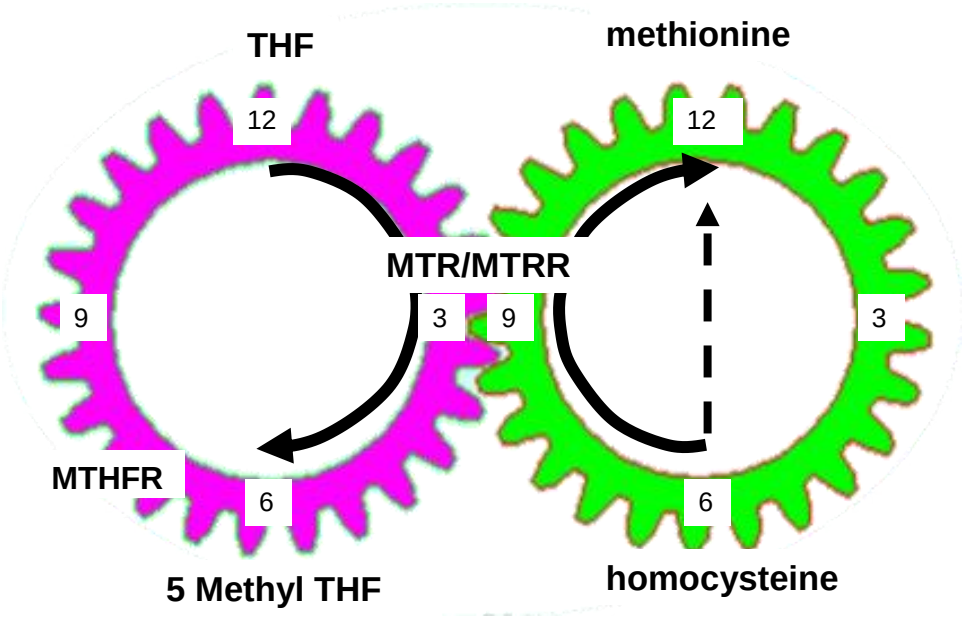
The role of FolaPro, intrinsic B12, nucleotides and folinic are to help to compensate for the methylation cycle mutations. This should open up the pathway, and in doing so will allow the proper expansion of T cells to aid in viral elimination. It is for this precise reason that we ask you to WAIT to add these supplements, until the body has had a chance to rebalance in Step One, and then have the immune support necessary in Step Two before beginning a detoxification process.

There seems to be a tremendous amount of confusion in the literature concerning 5 methyl folate. Only 5 methyl folate will bypass the MTHFr mutation; 5 formyl folate has other advantages, but it will not bypass the mutation. In order to go from 5 formyl THF to 5 methyl THF requires MTHFr. The product called FolaPro is clearly 5 methyl THF. There are products on the market labeled as folinic acid that are 5 formyl THF and others labeled folinic that are 5 methyl THF. Given the confusion, it is safer to use a product based on the chemical formula, rather than to use it based on its name on the label.

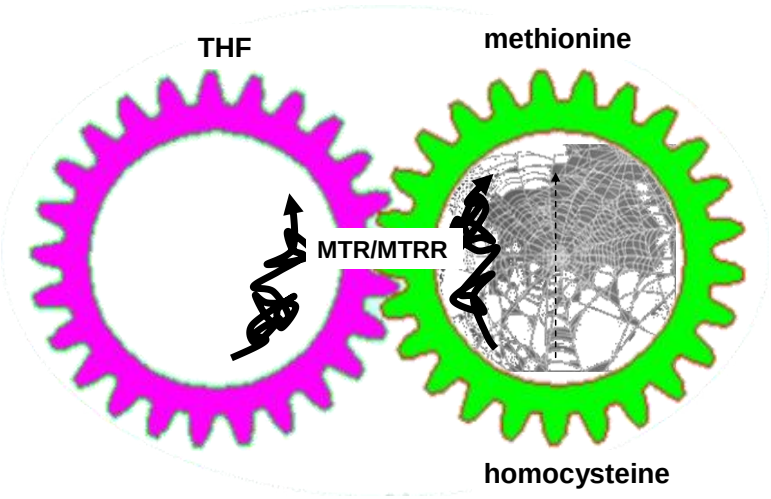


Dr. Amy Yasko
Ph.D, NHD, AMD, FAAIM, HHP, CTN

There are two pathways that will take you around the methylation cycle from homocysteine to methionine. The first is the "long way" around the cycle via the MTR and MTRR enzymes that requires B12 and the forward reaction of the MTHFR (where the C677T impairs the activity) for function. The other is a "short cut" through the middle of the cycle that bypasses MTR, MTRR and MTHFR via the BHMT enzyme. If you think of this portion of the cycle as a clock, the BHMT enzyme can use phosphatidyl serine, phosphatidyl choline and TMG as substrates to go directly from homocysteine at 6:00 to methionine at 12:00 skipping 7:00 through 11:00. The use of phosphatidyl choline, phosphatidyl serine and TMG therefore help to bypass these mutations. This backdoor reaction (or short cut) generates more norepinephrine relative to dopamine. The BHMT enzyme is also triggered by stress. Imbalances in dopamine relative to norepinephrine have been implicated in ADD and ADHD behaviors.

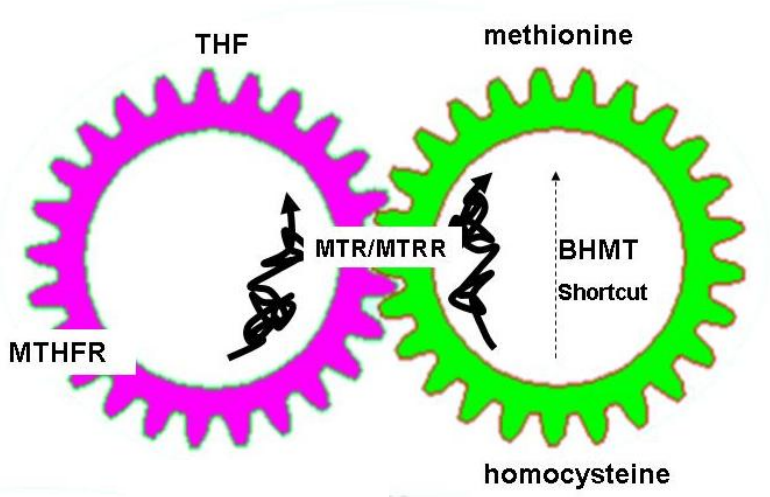


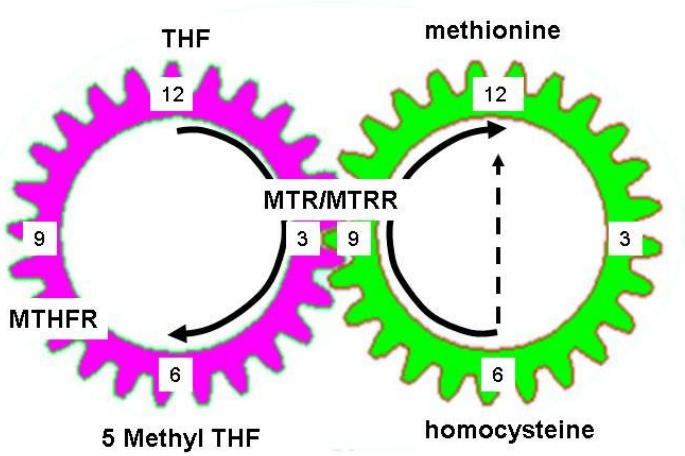
Initially it is simply important to get the methylation cycle moving again for individuals with mutations in these pathways. If the pathway has not been able to function due to methylation cycle mutations it is as if it has accumulated cobwebs. It is important to get the cycle working gain, and the fastest route to do this is by supporting the "short cut" through the BHMT enzyme.



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

It is faster to support this backdoor reaction, or shortcut to get the cycle working again.





Over time, as you are able to support MTR, MTRR and MTHFR C677T mutations so that the long way around the cycle can function properly then the body will not need to rely as heavily on the shortcut through the BHMT enzyme. Once the methionine levels appear to be more in balance on a urine AA test, and the methylmalonic acid levels are in normal range, and the FIGLU is in normal range it is time to consider looking at the use of DMG. The use of DMG is helpful in slowing the reaction through the BHMT enzyme and favoring the long way around the methylation cycle. Obviously it is essential to have supported any MTR, MTRR and MTHFR C677T mutations and run tests to look at pathway function before looking to make this shift.

There are some advantages to supporting the pathway so that you are able to go around the cycle, i.e. the “long way” as well as having the ability to take the “short cut”. As a result I do think it is important to supplement with low doses of a range of supplements that support all of the weak points of the methylation cycle. This would make sense as the building blocks for RNA and DNA are part of the reason you want to go the “long way” around the cycle. Using the BHMT enzyme to go from homocysteine to methionine will not help to generate RNA and DNA building blocks. This makes it difficult to repair new tissues or to expand T cell clones in response to infection. By adding RNA and nucleotides we take some of the pressure off the "long way" around the cycle so that we are not asking for as much activity via MTR and MTRR to generate the RNA and DNA building blocks. In a similar way by adding low dose folinic (1/4 Intrinsic B12 is the source for this) and low dose 5 methyl THF (¼ FolaPro) we help to supply additional intermediates that would normally be generated by the "long route" around the cycles. The nature of the MTHFR A1298C mutation suggests that supporting with FolaPro will also help this enzyme to support adequate levels of BH4.

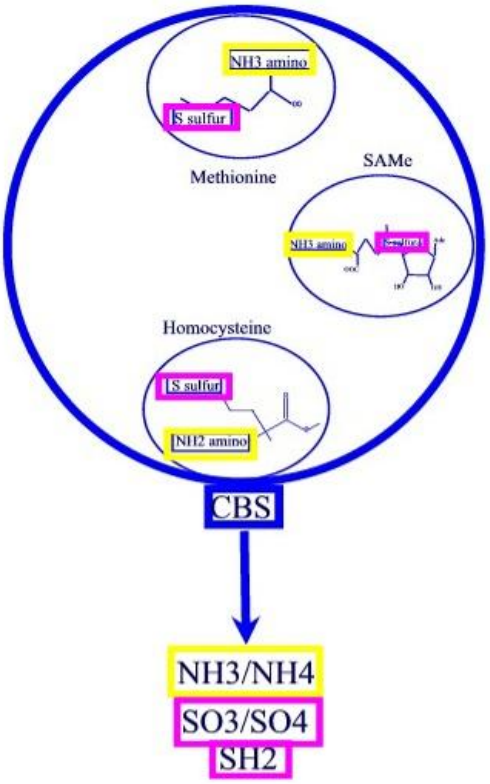
For individuals with CBS up regulation (+) it is important that the CBS/ammonia situation be the primary starting point. To refresh your memory, the CBS enzyme basically acts as a gate between homocysteine and the rest of the transsulfuration pathway. While we normally think of mutations in terms of shutting off or decreasing enzyme function, these particular mutations increase the activity of the enzyme. Going back to the analogy with the gate, it is as if the gate is constantly open. This will allow support that we use for the rest of the methylation pathway to drain through the CBS enzyme into the transsulfuration pathway, including any B12 we add to address MTR and MTRR mutations or FolaPro and Intrinsic to address MTHFR mutations. Unfortunately this “open gate” is not a neutral situation. While there are some positive end products that are generated via the transsulfuration pathway such as glutathione and taurine, there are also negative byproducts such as excess ammonia and sulfites. In order to detoxify this ammonia it requires the urea cycle, and uses BH4 and manganese that are needed for other functions in the body. In order to detoxify the sulfites it requires molybdenum. This leaves less molybdenum to help to address the zinc/copper ratio. On a related note, sulfur that is generated by all of the excess CBS activity has the ability to help to trigger this stress response. Chronic stress (the cortisol response) then up regulates the pathway via the BHMT enzyme. Until you get excess sulfur under control for the

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

CBS mutations it may be necessary to add even more support for this alternate pathway (via the BHMT enzyme) early on, to prevent this aspect of the pathway from becoming depleted due to stress.

Since the level of cysteine determines if taurine or glutathione is produced, an open gate (due to CBS up regulations) tends to favor high level production of taurine. By default, this will tend toward lower levels of glutathione, as the pathway is shunted in the direction of taurine production rather than glutathione production. The use of low doses of curcumin is often helpful in shifting the synthesis to glutathione rather than taurine, in conjunction with the use of Ammonia Support Formula RNA. Initially, I do not suggest the use of high level glutathione or NAC until the CBS issue has been addressed, as both of these supplements are sulfur donors. My experience has been that individuals with CBS up regulations are less able to tolerate both sulfur donors as well as lipid based support. Part of the reason for this intolerance to sulfur support, including sulfur based chelation, is that a net result of CBS up regulations (the open gate) is that intermediates of the methylation cycle are converted to toxic sulfur byproducts by all of the increased transsulfuration pathway activity. When sulfur groups are tied up in amino acids such as homocysteine, methionine, SAMe, SAH, cysteine the sulfur is not free to create havoc in the system. By virtue of increased CBS activity, these sulfur groups that were complexed as part of the methylation cycle in the form of amino acids, are now released into the system as sulfites which are toxic to the body and deplete much needed molybdenum from the system. A quote from Ingenblee and Young *(*Nutrition Research Reviews, December 2004) helps to eloquently describe this relationship *"Adaptive conservation of N and S body stores is reached by a functional restraint of the trans-sulfuration cascade, through the depression of cystathionine -synthase activity. As a result, upstream accumulation of homocysteine favors its re-methylation conversion to Met which helps maintain metabolic pathways of survival value."*

By looking at diagrammatic representations of the methylation pathway and relating the effects of genetic polymorphisms to biochemical pathways, it is possible to draw a personalized map for each individual's imbalances which may impact upon their health. By identifying the precise areas of genetic fragility, it is then possible to target appropriate nutritional supplementation of these pathways to optimize the functioning of these crucial biochemical processes



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

- **Step 1 Support**

The suggested supplementation that was listed in the customized MPA that you received represents the beginning of Step 2 of the program that I utilize in my practice. It assumes that you have already balanced systems as part of Step 1 as discussed in the autism book, the DVDs and the Supplement video. I recommend that you continue with supplements to balance organ systems that were started as part of Step 1, as you incorporate the suggestions from this document, your MPA and any additional testing, so your body can detoxify naturally. Below is a guide that may be helpful in aiding you in choosing supports.

Indications for Organ Support: Lab tests indicating a need for supports

Please note: It is NOT necessary to run every lab test mentioned or to use every supplement listed. The purpose of this list is to help you to determine the type of organ support needed f the program based on lab tests that you have already run and have in your files.

1) a) **Lab Tests indicating a need for Liver Support:**
- Elevated AST (SGOT)
- Elevated ALT (SGPT)
- Elevated alkaline phosphatase (ALP)
- Elevated lactate dehydrogenase (LDH)
- Elevated billirubin
- Elevated cholesterol
- Elevated triglycerides
- Long term chelation with sulfur based chelating agents
- High level excretion of toxic metals on fecal tests

b) Supports for Liver Health:
- Liver Support Formula RNA
- MTHFR A1298C+/Liver Support BH4 Compd
- Ultimate B Complex
- Folazin
- Cod Liver Oil -CLO
- Shark Liver Oil - Norwegian Shark Liver Oil
- SAM-e (Low dose in Ultimate B, ACAT/BHMT, COMT/VDR, MethylMate, and UltiFend)
- Rosemary (In NaturoMycin Spray, COMT/VDR, VDR FOK, UltiFend and Vita D-Light Spray)
- Quercetin 500 Plus (In UltiFend and COMT/VDR)

2) a) Lab Tests indicating a need for Kidney Support:
- Elevated BUN
- Urine excretion/detox of metals for prolonged periods

b) Supports for Kidney Health:
- Kidney Support Formula RNA
- CBS/NOS Compounded Supplement
- Cranberry Caps (In UltiFend and NaturoMycin Spray & Caps)
- Cranberry Juice -Sweeten with Xylitol or Super Stevia
- Curbita Bladder Caps (In NaturoMycin Caps)
- SAM-e (Low dose in Ultimate B, ACAT/BHMT, COMT/VDR, MethylMate A, and UltiFend)
- ATP-20 (In MitoForce and MTR/MTRR/SUOX

3) a) Lab Tests indicating a need for Pancreatic Support:
- Consistently elevated glucose
- Consistently low glucose
- Elevated triglycerides
- VDR Fok + - or VDR Fok + +
- Imbalances in pancreatic elastase on a CSA/GI
- Imbalances in chymotrpsin values on a CSA/GI
- Imbalances in SCFA (Iso-butyrate, iso-valerate and n-valerate) on CSA/GI
- Imbalances in LCFA on a CSA/GI

b) Supports for Pancreatic Health:
- Prolongevity Formula RNA
- CCK Support Formula RNA
- VDR FOK Compounded Supplement
- Vita D-Light Spray OR Vitamin D
- Special Digestive Enzymes With Each Meal
- Fenugreek
- Chromium
- Vanadyl
- GABA

4) a) Lab Tests indicating a need to Decrease Calcium:
- Elevated calcium relative to magnesium on a urine essential element test
- Elevated calcium relative to magnesium on a red blood cell element test
- Stims

b) Supports to help address High Calcium:
- MitoForce Compounded Supplement
- CoEnzyme Q10 Fatigue & Muscle Support Spray
- GSH Capsules OR Glutathione Chewing Gum
- Magnesium (Low dose in MetalAway, MTR/MTRR/SUOX and MitoForce)
- Chamomile
- Boswellia -Ayur Boswellia Serrata (In Inflammation compound-coming)
- Vinpocetine
- Zinc (Low dose In NaturoMycin Spray, SeroMood and PeptiMycin)
- Paradex (In NaturoMycin Caps)
- Don Quai - Max V
- Air Power
- Black Cohosh
- Prevagen 5mg or less

5) a) Lab Tests indicating a need to Increase Calcium:
- Calcium below the range of low end normal on a urine essential test
- Calcium below the range of low end normal on a RBC element test
- High level excretion of lead should check urine calcium levels

b) Supports to Increase Calcium:
- Bone Support Formula RNA
- MitoForce Compounded Supplement
- CoEnzyme Q10 Fatigue & Muscle Support Spray

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

GSH Capsules OR Glutathione Chewing Gum
Nettle (In Calm Down-Gaba/Glutamate Spray)
Chamomile
Chervil
Cal/Mag/VitD/VitK -Calcium & Magnesium Citrates
Don Quai - Max V
Black Cohosh
Prevagen 5mg or less

6) a) Lab Tests indicating a need for Glutamate/GABA balance:
Elevated glutamate, glutamine, glutamic acid on urine AA
Elevated aspartate, aspartic acid on urine AA test
Low GABA (gamma aminobutyric acid) on a urine AA test
Low GABA on a Neurotransmitter test
Elevated quinolinic on OAT/Metabolic Test
Seizures
Stims
Poor eye contact
Aggressive behavior

b) Supports to balance Glutamate/GABA:
Nerve Calm Formula RNA
Comfort RNA
Glutamate/Gaba Spray(Calm Down)
Melatonin Sleep Spray
Progesterone cream- Pro-Gest Body Cream
GABA
Pycnogenol
Grape Seed Extract
Valerian Root
Jujube
Lithium Orotate based on UEE levels
L-Theanine
Taurine (not for CBS + or SUOX Mutation unless suggested on testing)

7) a) **Lab Tests indicating a need for Immune Support:**
Imbalances on ImmunoSciences or other similar test panels

b) **Supports for the Immune System/Thymus/Spleen**:
Liver Support Formula RNA
AHCY/SHMT Compounded Supplement
Immuno Forte
Ora-Triplex
Ultimate B Complex
Mycoceutics mushroom w/beta glucan
Transfer Factor Classic-4Life
Spirulina

8) a) **Lab Tests indicating a need to address Bacterial Imbalances:**
History of chronic ear infections
Maternal history of Streptococcal infection
History of bacterial pneumonia
Streptococcus, E coli on CSA/GI
Other bacterial pathogens on CSA/GI
Elevated kynurenic on OAT/Metabolic Test, CONFIRM with CSA/GI
Elevated quinolinic on OAT/Metabolic Test, CONFIRM with CSA/GI
Low gut pH or high gut pH
High suberic on a MAP or OAT
High DHPPA on a MAP or OAT

b) **Supports to balance / repopulate GI Tract/ Decrease E.coli and Strep:**
Bowel Support Formula RNA
Super digestive enzymes
VDR/ Fok compound
MTHFR A1298C caps
CCK Support RNA
Microbial Support Formula RNA
Stomach pH Balancing Formula RNA
IMF 5 (Immunfactor #5)
AHCY/ SHMT caps/Spray
Grapefruit seed extract
Slippery elm
VitaOrgan
Leaky Gut RNA
Glucosamine/chondroitin plus
Rotate probiotics (one each day of the week):
NutriClean Probiotics
Supremadophilus
Florastor
Allerdophilus
Lactobacillus Reuteri(Gut Health or probiotic drops)
Lactobacillus Plantarum
FloraElite
Rotate antimicrobial herbs (choice based on CSA Sensitivity tests):
NaturoMycin Spray
NaturoMycin Caps
Bactisolve
Additional individual herbs as indicated by sensitivity testing

9) a) **Lab Tests indicating a need to address Yeast Imbalances**:
Elevated arabinose on OAT/Metabolic test, CONFIRM with CSA/GI
Presence of yeast on CSA/GI
Low gut pH, CONFIRM with CSA/GI

b) **Supports to balance / repopulate GI Tract/ Decrease Yeast:**
Rotate probiotics (one each day of the week):
NutriClean Probiotics
Supremadophilus
Florastor
Allerdophilus
Lactobacillus Reuteri(Gut Health or probiotic drops)
Lactobacillus Plantarum
FloraElite
Candisol
IMF 7 (Immunfactor #7)
Lactoferrin
Nautromycin Spray
Naturomycin Caps
BActisolve
Stomach pH Balancing Formula RNA
CCK Support RNA
Mycology Support Formula RNA
Buffer pH supplement

10) a) **Lab Tests indicating a need to Address Parasites:**
Parasites on a CSA/GI

b) **Supports to address/balance parasites:**
Paradex
Naturomycin Spray and caps
MTHFR A1298C caps

11) a) **Lab Tests indicating a need to address Helicobacter:**
Helicobacter test

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

Presence of Blood on a CSA/GI
Low manganese on UEE or Hair metals test in spite of supplementation
Very High Suberic on MAP
Extreme swings in CSA/GI profile Stool PH
High asparate Or High tryptamine on NT
Excretion of bismuth on a FMT in the absence of supplementation
Consistent cadmium excretion on a UTM and FMT
Signs of ketosis on a MAP
Arginine 50+ when all other UAA's (except Taurine) are to the left of 50
Low PS on a UAA regardless of having all suggested supports in place
High 5HIAA or Indole acetic acid on a MAP
High Taurine on UAA in the absence of a CBS +, OR in spite of sufficient CBS RNA/Ammonia RNA

b) **Supports for Helicobacter:**
Bowel RNA
HELX RNA
Liver Support RNA
MTHFR A1298C/liver Compounded support
B12 oral spray + B12 liquid drops + additional B12
PeptiMycin Compounded Supplement
SHMT spray
Adenosyl B12 mega drops
Reservatrol Spray
Ester C
E-Gems Elite
GSH
Broccoli Max
Air Power
Baking Soda with meals
Mastica Gum
Low dose thiocyanate + hydroxy B12
NAC
Some cases very low dose Arginine
Serraflazyme with meals
Intrinsic factor
Coffee
L-Carnitine
Huperzine (based on testing)

12) a) **Lab Tests indicating a need to Support Inflammatory Imbalances**:
Elevated chymotrypsin test levels
CRP above normal range on blood work
Elevated IL 6 on blood work
Elevated TNF alpha on blood work
Chronic bacterial infection
Low gut pH
Allergic Rashes

b) **Supports for the body to balance Inflammatory Mediators:**
General Pathway Support RNA (Health Foundation)
Hyper-Immune Balancing Formula RNA(not for COMT ++)
Cytokine Balance Inflammatory Pathway Support RNA
Stress Foundation Formula RNA
Heart Support RNA
Bowel Support RNA
Inflammation Compounded Supplement
Nettle
Boswellia-Ayur Boswellia Serrata
Turmeric
Skull Cap
Chamomile
Quercetin 500 Plus
Petadolex -Butterbur
Cherry Fruit Extract

13) a) **Lab Tests indicating a need to address Zinc/Copper Ratio:**
Elevated copper relative to zinc on a urine essential element test
Elevated copper relative to zinc on blood work
Low levels of ceruloplasmin on blood work
Red hair, CONFIRM with a essential mineral test

b) **Supports for Zinc/ Copper balance:**
Magnesium
Zinc (Lozenges, drops, Krebs zinc)
Molybdenum
Chromium Picolinate
Lithium Orotate
Selenium
Strontium
Boron
Manganese
Vanadyl
Cell Food for Copper support as recommended on testing
Sodium: Aerobic 07
Potassium: Aerobic K07 or Potassium Citrate
Phosphorus (complexed)
Carnosine
Rosemary
Zinc
Krebs zinc
EDTA
EDTA SOAK

14) a) **Lab Tests indicating a need to address Glutathione or low Sulfur values:**
Low glutathione on tests (for low reduced glutathione(GSH) but high oxidized glutathione (GssG)
Consider NADH first, then rerun test for reduced glutathione levels)
GST polymorphisms
Low values on a hepatic detox profile
Low sulfur test values
Very high taurine on a UAA

b) **Supports for Glutathione/Sulfur:**
CBS RNA based on UAA taurine levels

* USE **LIMITED** support if you suspect a CBS up regulation*
SAMe
Alpha lipoic acid
Taurine
Broccoli
Garlic
Rosemary
Sublingual glutathione
Oral GSH glutathione
IV glutathione
Glucosamine/ MSM
Chondroitin sulfate
N-acetyl cysteine w/ quercetin
Vitamin C with Rose Hips(500mgc for every 250mg NAC)
Creams (transdermal):
Glutathione cream
Magnesium sulfate cream
Alpha lipoic acid cream
Glucosamine/ MSM cream

15) a) **Tests indicating a need to address Mitochondrial**

Support/Krebs cycle:
Elevated suberic on OAT/Metabolic analysis test
Low levels of Krebs cycle intermediates

b) **Supports for Mitochondrial/Krebs Energy:**
MTHFR A1298C+/Liver Support BH4 Compd Sup
MitoForce Compounded Supplement
MetalAway Compound Supplement
CoEnzyme Q10 Fatigue & Muscle Support Spray
GSH Capsules OR Glutathione Chewing Gum
Potassium Krebs Magnesium-Potassium Chelates
Riboflavin
L-Carnitine
Malic Acid
Magnesium Citrate

16) a)**Lab Tests Indicating a Need to Address Lithium:**
High Lithium on UEE or very low lithium on UEE
Low Lithium on HM or dumping of lithium on a HMT
Aggression
Lack of cobalt on a UEE in spite of high level support
MTR + status

b) **Supports for excretion of high levels of Lithium**
AHCY/SHMT Compounded Supplement
MTHFR A1298C Compound Supplement
VitaOrgan Compound
SHMT spray
Low dose Lithium Orotate (work with your Dr)
Ultimate B Complex
GSH capsule OR Glutathione Chewing gum
CellFood
Folazin
BioNativus Trace Minerals
Frequent testing of UEE & Hair Metals Tests to check on lithium levels
Topical iodine tests on a regular basis
CHECK taurine levels on a UAA, CBS OR Ammonia
RNA as needed

17) a) **Lab Tests indicating a need to focus on Potassium**
Very low potassium on a HMT
Pattern of potassium dumping on UEE and HMT
Very low rubidium on a HMT

b) **Supports for Potassium**
Krebs potassium
Potassium citrate
Mitoforce compounded supplement

- **Mineral Support**

Even before working to actively excrete toxic metals from the body it is important to be sure that essential minerals are in balance in your system. This is especially important as you transition into Step 2 of the program because as you support the methylation cycle in the body, it restores the body's natural detoxification abilities. This can result in detoxification of virus, metals and bacteria that have accumulated in the body over time. This natural ability to detoxify is a separate function from active chelation therapy.

It is possible to use the following analogy to understand the distinction. You can think about the way the body handles toxins as a revolving door (the kind you see in office buildings or hotels). Toxins come in and toxins come out over the course of our lives. That is how most of us survive in a world filled with toxins. For individuals with methylation cycle mutations the revolving door is not working properly; toxins come in but they don't go out. Instead they accumulate. When you use a chelating agent, you are taking the toxins out the side door of the building. However the revolving door is still broken. Although the use of chelation can enhance the removal of toxins from the body, it cannot repair the revolving door. As a result toxins can still continue to accumulate in spite of chelation. Over time, especially if you stop chelating, you run the risk of toxins building up again unless you fix the broken door. Running nutrigenomic tests help you to know what you need to do to fix the broken door so that it will work properly.

Regardless of whether you are using chelation therapy to speed up the detoxification process or simply supporting the methylation cycle to prevent health conditions that can occur as a result of methylation cycle mutations, using nutrition to bypass mutations can lead to detoxification of the body. These are natural detoxification systems that operate on a regular basis for all of us, provided that our revolving door is functioning properly. For those whose revolving door is broken, once you do start to supplement for mutations you may find an increased level of detoxification from your system. This is especially true if your revolving door has been blocked for a long time. The use of urine, stool and blood toxic metal tests is one way to monitor the excretion of these metals and to verify that any symptoms you experience are related to natural detoxification. It is also important to monitor essential minerals in the body at the same time. I have noted that when we see excretion of heavy metals we often see a drop in essential minerals at the same time. This is why it is a good idea to follow essentials as well as toxic metals especially when you are seeing large amounts toxins on the toxic metal reports.

Excretion of mercury can affect the levels of lithium and iodine. It is possible to support iodine using 1/4 iodoral or other natural forms of iodine and to support healthy lithium levels with 1/4 lithium oratate. Decreases in calcium are often observed following the excretion of lead. Calcium can add to excitotoxin activity; consequently I prefer that calcium levels stay in the lower range of normal for those individuals with conditions that include elevated glutamate. If calcium support is needed I suggest utilizing herbs that include other components that may help to calm the body while increasing the level of calcium at the same time such as nettle, chamomile and chervil. If this is not sufficient to increase the levels within normal range then a supplement that includes calcium as well as magnesium and vitamins D and K is the preferred way

to supplement. Calcium should be balanced by magnesium to help to prevent excitotoxin activity and vitamin D and K help to ensure the proper transport of calcium in the body. Chickweed, nettle, dandelion leaf and yellow dock are very nice natural sources of boron. The level of boron may drop along with calcium when you are excreting lead. Chickweed is also helpful for skin rashes, nettle helps to decrease inflammatory mediators and may also increase serotonin, dandelion leaf is supportive for the kidneys and yellow dock helps to support regular bowel movements. I prefer a mixture of small amounts of all of these to support boron if needed. However, I have listed some of the other benefits of these herbs to help you in choosing a single one from the list if needed.

Magnesium can be supported as magnesium citrate, which is a very absorbable form and also will support citrate in the body or with a number of other products. Zinc can trigger activity at glutamate receptors in high doses. As a result I choose to keep zinc at 40mg per day or lower. I have supported zinc with zinc picolinate, zinc, as well as zinc as a Krebs cycle intermediate. I prefer to keep magnesium levels higher than calcium so that the ratio favors more magnesium than calcium. Similarly I prefer that zinc levels exceed that of copper so that the relative ratio is in favor of zinc.

There are a wide range of choices to support molybdenum and selenium. Healthy molybdenum levels are important to aid in sulfite detoxification and selenium is useful in binding to mercury. Molybdenum levels can be easily depleted in individuals with CBS up regulations.

Excess ammonia (generated by the CBS up regulations) can also deplete manganese stores in the body as manganese is needed to help to detoxify ammonia. Classic signs of chronic manganese deficiency include low cholesterol, elevated alkaline phosphatase levels and depressed T cell mediated immune function (due to thymus issues). In addition manganese is needed to produce dopamine as well as for vitamin C to function in the body. The pancreas requires manganese for insulin production, and a lack of acetylcholine and difficulty entering the Krebs cycle is related to low levels of manganese. It is particularly important to monitor manganese levels as well as molybdenum levels for individuals with CBS mutations. In addition we tend to see low levels of manganese (along with low boron and strontium) for individuals who have the SUOX mutation or those who have such low levels of B12 that they may have “functional SUOX” deficiencies.

It is important to pay attention to the level of essential elements and support to keep them in balance. For overall general mineral support I often suggest BioNativus trace minerals along with Cell food, using only two to three drops of each per day.

- ## Using Your Information

By this point you should have your Step 1 support in place, basic mineral support in place and have a general understanding of the importance of the methylation cycle and why you want to supplement to bypass mutations. While the MPA gives you a quick color coded chart to help to guide you with the level of support needed, I do think it is important for you to understand how to read your own test results. Understanding which SNPs are an issue for you based on your nutrigenomic test results will also help you to use this information to its full advantage. By looking at your nutrigenomic test, and identifying which SNPs are a concern, you will know which sections of this document applies to you personally. You can then focus on those sections of this document that are directly relevant to your personalized test results, and be in a position to have a better understanding of “**why**” certain supplements have been suggested for your consideration on your MPA. Reading through this document should help to give you the knowledge, which translates into power over your own health and enables you to make decisions regarding your personal supplement program.

- ## Step 2 Basics

The purpose of Step 2 is to support the body to allow for excretion of toxic metals through the release of chronic viral and bacterial infection in the body. This is based on the theory put forth in The Puzzle of Autism book that bacteria helps to retain aluminum in the body and the chronic viral infections allow for heavy metal accumulation. Step 2 begins by looking at the nutrigenomic profile to bypass methylation cycle mutations with the use of supplements. Since the methylation cycle is so critical to silencing virus, and supporting the immune system, simply allowing the methylation cycle to function is often enough to allow for viral, bacterial and metal detoxification.

1) Address CBS/ammonia imbalances using the ammonia support program. This is an important first step so that added methylation cycle support does not lead to increased levels of ammonia, hydrogen sulfide and other toxic sulfur byproducts. If there are no CBS up regulations you can skip this step

2) Wait at least one month after (1) before looking to add the rest of methylation cycle support as indicated by the nutrigenomic profile. During this time period you can look at integrating the use of the comprehensive gut/bacterial support program while the CBS/ammonia issues get in better balance.

.

3) Support the rest of the methylation cycle imbalances using support for both pathways around the methylation cycle. You are looking to support the "long way" around the cycle via the MTR/MTRR as well as the "short cut" through the cycle via the BHMT enzyme.

4) Creatinine levels will increase as a function of proper methylation cycle function as well as by virtue of the decreased ammonia levels as CBS up regulations are addressed. Increased creatinine will cause detoxification reactions.

5) Increased beta alanine, anserine, carnosine may be seen as the "short cut" around the methylation cycle is supported as and ammonia levels drop.

6) Once the levels of beta alanine, anserine, carnosine drop you can consider the addition of DMG. This will emphasize the long route around the cycle rather than the short cut.

7) Add in metals RNA program if needed.

It is important to note that when we have ACAT and SHMT mutations that you can also look to begin by supporting to bypass the ACAT and SHMT issues even ***prior*** to addressing CBS. This is certainly worth considering in individuals who have more severe gut issues, those who tend to have a number of imbalances on CSAs or have muscle weakness which may be related to aluminum retention. I have found that working to support ACAT and SHMT can have a positive impact on the gut balance and so this can be the starting point for nutrigenomic supplementation for those who have ACAT and SHMT mutations and where the gut is a major issue.

SNP Specifics:

- **ACAT Support**

ACAT, or acetyl-Coenzyme A acetyltransferase can affect the pathways we are looking at in several ways. First ACAT plays a role in cholesterol and other membrane lipid balance. Bile salts have been shown to increase ACAT activity, so that is why we look at the use of cholacol for those with ACAT issues (for instance Erikson et al, Lipids Oct 30, 1995). In addition I have suggested the use of policosanol to help with membrane lipid balance and fluidity. I have written posts in the past about the role of membrane fluidity and how it may impact on neurological function. Bile acids are synthesized from cholesterol and then conjugated to taurine. The high taurine levels that we are seeing in those with ACAT may reflect a lack of bile acids for conjugation. The use of cholacol appears to be making a positive difference in that regard.

The next portion of the pathway that may be impacted by ACAT is the level of acetyl CoA. Remember that acetyl CoA feeds into the top of the TCA cycle at 12:00. For this reason I am suggesting that you consider benfotiamine, riboflavin, and pantothenic acid all of which help the reactions between pyruvate and the TCA cycle. In addition, the use of low dose ALA (Alpha Lipioc Acid) may be helpful as it has been shown to replace acetyl CoA in certain reactions (Wagh et al J. Biosci. Vol 11, 1987). A small amount of the ALA supplement (a sprinkle) or the topical ALA with green tea lotion are some options for low dose ALA. In my personal opinion, more is not always better when it comes to support with ALA. So it will be important to find a balance in terms of the level of ALA that helps to support ACAT without adding so much that we find an impact on excretion. There are however cases where high dose ALA has been reported to have wonderful effects (work by Andrew Cutler) so the use of ALA needs to be an individual decision based on the genetics as well as the biochemical lab data that we use as feedback.

A block at the acetyl CoA point of the Krebs/TCA cycle can also lead to an accumulation of oxalates. In order to keep the cycle moving, it is important for the oxalates at 11:00 to combine with acetyl CoA coming in at 12:00 to keep moving around the cycle. The kinds of support that we often use to address this can be considered including at a minimum vitamin K (Super K) and lactoferrin.

A block at this point can also lead to increased levels of MMA (Methylmalonic Acid). For this reason I have suggested similar support for ACAT that I do when I see high levels of MMA. This includes adenosyl B12 (Dibencozide), other forms

of B12, low dose vitamin E succinate, lactoferrin, a sprinkle of actifolate and nucleotides. MMA may inhibit succinate CoQ reductase. This enzyme is important in electron transport. That is why I have suggested vitamin K (menaquinone) as well as CoQ 10 (ubiquinone) to help to serve as electron acceptors when we have high MMA or with ACAT issues.

From a biochemical standpoint, we see higher levels of methionine with ACAT mutations. For this reason I am looking to support the conversion from methionine to SAMe. Cholacol, GSH and CoQ10 are all supports to consider for the MAT enzyme (Methionine S-adenosyltransferase). Again, remember that curcumin and quercetin may help to shift the transulfuration pathway toward GSH. Doing this by working within the system rather than simply adding support may be an advantage as too much GSH can feedback and inhibit GCL (glutamate- cysteine ligase) which is the enzyme that shunts to glutathione rather than taurine after cysteine. So, as always we look to add in moderation and in a balanced fashion.

- **AHCY Support**

AHCY is the enzyme that converts S-adenosyl homocysteine (SAH) to adenosine and homocysteine. Based on results of biochemical tests, the SNPs that we look at in the AHCY gene appear to cause a decrease in enzyme activity. Decreased AHCY activity should lead to lower levels of homocysteine and it would be expected to cause higher levels of SAH. However, what I have observed from biochemical test results would indicate that it is not this straightforward of a situation. What preliminary data indicates is that ***once methylation cycle support is in place***, what we actually observe for those with AHCY mutations is higher methionine, higher SAMe relative to SAH and higher relative glutathione levels than would be expected. Since SAH is a known inhibitor of COMT, those who are AHCY + may actually have less inhibition of their COMT activity and therefore be in greater need of methyl donors. This too would fit with some of the clinical data that I am seeing. I realize that this is complex and confusing and I am working to characterize and move forward on these SNPs in areas where there is very limited work, so please realize that this information is based on preliminary clinical data and may change and evolve over time. However, looking at published literature we can find additional data that would support what I am seeing from our clinical data.

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 methyltransferase 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. Reports in the literature suggest that SAMe helps to stabilize the CBS enzyme and can increase its activity by 2 to 3 fold. This is a mild effect on CBS when compared to the 40 fold increase that has been reported for CBS C699T. In general we do not see excessively high taurine levels for those with AHCY mutations and there are indications that these more moderate levels of taurine may be related to healthier glutathione levels (for individuals supplementing to bypass any other methylation cycle mutations), as would be expected. (PNAS 2008, 103:17; Theoretic Biology and Medical Modelling 2008, 5:8; JBC 2002, 277:41; Jnutrition 2002,132)

For those who are CBS + as well as AHCY +, based on preliminary data it appears thus far that the effect of the AHCY mutation is partially masking the effect of the CBS up regulation. By limiting SAH activity, the amount of homocysteine available to the CBS enzyme would also be limited, which in turn would limit the amount of cysteine and allow for glutathione synthesis rather than higher taurine levels. So, in spite of low level increased CBS activity (2 to 3 fold) by the increased SAMe that is generated from the AHCY mutation, the limiting amounts of homocysteine that are generated may be the dominant factor here in allowing for more glutathione relative to taurine.

The bottom line is that for those with AHCY mutations it may be especially important to monitor UAAs in order to balance the effects of AHCY mutations, CBS up regulations and other methylation cycle mutations on the system. In addition, for a number of individuals we also have glutathione, SAH, SAMe levels that have been useful. Between a clear sense of nutrigenomic testing and follow up biochemical results we can work to keep the system in better balance, both for those with AHCY mutations as well as other mutations in this pathway.

- **BHMT Support**

The SNP panel looks at four different mutations in the BHMT gene, BHMT 1, 2, 4 and 8. Based on differences in biochemical testing the recommendations for support to bypass BHMT issues are slightly different. Remember that BHMT is the enzyme responsible for the "short cut" around the methylation cycle. It is important to get this pathway moving initially, then once we have sufficient B12 (and the rest of methylation cycle support in place) to look at shifting the focus to the "long route" around the cycle, while still maintaining BHMT support.

BHMT 8 appears to be a SNP that causes an increase in the level of MHPG(3-methoxy-4-hydroxyphenylglycol) on a MAP test relative to dopamine breakdown (HVA)(homovarillie acid) and may be related to attention issues. The Attention Support formula RNA seems to help with this balance along with the use of PS/PE/PC(Phosphatidyl Serine Complex), low dose SAMe and NADH.

BHMT 1,2 and 4 do not appear to cause similar increases in MHPG and also do not seem to be as highly associated ADD/ADHD type behaviors. However, those with BHMT 1,2 and 4 mutations often show increased taurine levels on a MAP test as well as increased levels of short chain fatty acids on a CSA test. Support that is similar to what is suggested for ACAT mutations seems to help balance the CSA tests and low dose Ammonia Support Formula RNA can also be helpful.

- **CBS +**

One of the nutrigenomic markers that can have the biggest impact on the supplement program is the presence or absence of a CBS up regulation. CBS up regulations can play a major role in the function of the methylation cycle. This mutation can allow for any added methylation cycle supplements to be depleted through the transulfuration pathway to generate additional ammonia and excess sulfur compounds. This creates a "catch 22". It is important to supplement the methylation cycle in order to address viral infection in the body, toxic metal burdens as well as to support neurotransmitters and immune function and myelination of nerves. On the other hand, until the CBS up regulation is under control, there is a risk of any added methylation cycle support creating additional problems in the body. The added ammonia that is generated due to enhanced breakdown of methylation cycle intermediates will put a burden on the urea cycle and will deplete BH4 that is needed for serotonin, dopamine, conversion of phenylalanine to tyrosine and language related function. The excess sulfur can trigger the stress/cortisol response in the body as well as potentially causing a decrease in the enzyme glucose 6 phosphate dehydrogenase (G6PDH). The A1298C mutation in the MTHFR gene can further impact the levels of BH4.

Adequate levels of BH4 can be visualized as a stool with three legs. One leg can be labeled "CBS up regulations". The second leg can be labeled "MTHFR A1298C" and the third leg can be labeled "chronic bacteria/aluminum". In order to have a stable stool, or stable BH4 levels it requires that all three legs be sturdy.

If we have CBS up regulations it can weaken one of the legs of the stool. The more total CBS up regulations the weaker that particular leg is. If there are MTHFR A1298C mutations this can impair a second leg of the stool. Chronic bacterial infection can lead to retention of aluminum which can cause issues with the third leg of the stool. Aluminum inhibits the enzyme that is needed to synthesize BH4. Between aluminum (due to bacterial infection) which inhibits the ability to make BH4, the A1298C mutation which I believe disrupts the ability to recycle and regenerate BH4 and the CBS up regulations which use up BH4 faster than it can be supplied, individuals who are CBS +, MTHFR A1298C + and have chronic bacterial and aluminum issues may be severely depleted in BH4. It is important to address all three legs of the BH4 stool by supporting the body to address chronic bacteria/aluminum, supporting the MTHFR A1298C mutation and addressing CBS/ammonia issues.

As already mentioned, BH4 is needed for neurotransmitter synthesis. The other side of having adequate levels of neurotransmitters is the rate of their breakdown. Bacterial infection triggers the breakdown of tryptophan (needed for serotonin). In addition the maoA status reflects the level of serotonin breakdown. Individuals who are maoA + + will breakdown serotonin more slowly, in an analogous fashion to the way in which COMT V158M + + individuals breakdown dopamine more slowly. These mutations may help to offset the decreased synthetic capacity due to low BH4 levels. The counter side of this benefit is that mood swings and aggression are seen more frequently in individuals who are maoA + + and/or COMT V158M ++.

The CBS up regulation may not only deplete the intermediates in the methylation cycle, it can also generally lead to elevated levels of taurine and excess sulfur groups. As a consequence it is ordinarily recommended that individuals with a CBS up regulations do not use high levels of taurine or additional sulfur donors (broccoli, etc) as it may create problems with excess sulfur groups. However, while the CBS up regulation should be causing high levels of taurine and ammonia in the system, in some cases we are not seeing that on the amino acid test. Since the level of methylation cycle support also

influences the results of the amino acid tests in terms of taurine levels, insufficient methylation cycle support can cause lower levels of taurine which can be misleading in terms of choosing support for the CBS up regulation.

Until we support the methylation cycle we are not going to see the full impact of the CBS up regulations.

On a regular basis after supplementation based on this nutrigenomic profile it is highly suggested that you run a follow up urine AA tests to confirm the levels of taurine and ammonia. This is important because if you are seeing elevated taurine and ammonia in the urine, it will be important to look at adjusting the level of ammonia support.

One of the roles of the transsulfuration pathway is to generate glutathione and taurine. The level of cysteine that is detected by the cell, determines if that cysteine goes on to make taurine or to make glutathione. Low levels of cysteine favor glutathione synthesis. High levels of cysteine lead to the synthesis of taurine. The reason we see such high level conversion to taurine with a CBS up regulation is that the cysteine generated is so high that the pathway is shunted toward taurine formation. Indications in animal models are that the CBS C699T represents a 40 fold increase in enzyme activity (the CBS A360A (C1080T) is not as strong of an up regulation). It is not surprising that it is often difficult to see appreciable levels of homocysteine, cysteine or cystathionine for some individuals with these CBS up regulations as there is such a rapid conversion rate ultimately to taurine. In many cases our best indication of the CBS up regulation on an amino acid test is the very high levels of the ultimate end products of taurine and ammonia.

Taurine is calming; it also helps to prevent seizure activity. For this reason we also do not want taurine levels to drop too low on a UAA test. Recall…until the entire methylation cycle is supplemented properly it may be impossible to judge the actual taurine level. Once support is in place to bypass mutations in the pathway and if we still see low taurine levels, then you may want to increase the taurine levels to normal range by a combination of stimulating the transsulfuration pathway a bit with low level B complex and finally, if necessary with direct taurine supplementation.

In order to address CBS up regulations it has been found that the use of a low protein diet, in conjunction with Ammonia Support Formula RNA will help to balance the system. In addition the occasional use of charcoal as a supplement just before bed has proven to aid in controlling excess ammonia levels. The best time for the use of charcoal is just prior to bed to separate the time frame of the addition of the charcoal from other supporting supplements. This should limit the ability of the charcoal to deplete the body of needed nutrients. It is important to be sure that the bowels are moving well with the addition of charcoal. The use of a magnesium citrate flush (high doses of magnesium citrate) following the addition of 1 to 2 charcoal capsules helps to ensure a bowel movement after this addition of charcoal to soak up excess ammonia. In addition the herb Yucca is reported to aid in ammonia support. I find that using yucca with protein meals is generally sufficient. The frequency of use of yucca as well as the charcoal should be dependent on testing of ammonia levels in the urine.

If you should find highly elevated taurine levels over time with continued monitoring of urine AA values, then I would suggest that you consider more frequent Ammonia Support Formula RNA can help to balance the system.

CBS C699T and A360A mutations can also cause a depletion of molybdenum levels as molybdenum is involved in making sulfur groups less toxic in the body as it is a cofactor for the enzyme sulfite oxidase. Increased amounts of molybdenum may be utilized in individuals with a CBS up regulations in response to the increased generation of sulfur groups via the transulfuration reaction. It may be hard to keep molybdenum in the normal range; this may account in part for copper/ zinc imbalances that are observed as the molybdenum cannot keep up. It is worth running an essential mineral urine test to be certain that molybdenum levels are in the normal range. If not, it would make sense to consider using molybdenum supplementation. On a related note, xanthine oxidase is another molybdenum requiring enzyme in the body. When milk and other dairy products are not homogenized, components of the milk are digested in the stomach and the small intestine, including the enzyme xanthine oxidase. However, when milk is homogenized, its xanthine oxidase is not broken down, but instead passes into the circulation. The elevated presence of xanthine oxidase may exacerbate limited molybdenum levels and add to further imbalances in the copper levels. This would also suggest that it is wise to continue with a casein free diet and if you are going to use any dairy products that it may be beneficial to use whole dairy products that are not homogenized particularly for individuals with CBS C699T and C1080T mutations. Molybdenum, EDTA, carnosine and zinc can help to keep copper/zinc ratios more balanced. Chewable zinc tablets with slippery elm may benefit the gut as well as providing a well controlled dose of zinc. Dosing can start with ¼ tablet and increase to 1 whole tablet per day. The liquid zinc or zinc capsules are also an acceptable alternative. The Kreb's cycle zinc is another option once glutamate and GABA levels are in balance. BioNativius trace minerals are useful for providing general mineral support along with additional support as needed from the zinc, molybdenum and magnesium. Essential mineral tests can be run from urine samples to verify that minerals are within range. Pay careful attention to lithium and iodine levels during

any detoxification of heavy metals as excretion of mercury can affect the levels of lithium and iodine. These essential minerals appear to play an important role in helping to balance mood swings that can occur as a result of dopamine fluxes. These dopamine fluxes are much more of an issue in individuals who are COMT V158M + + regardless of their VDR Taq status. If lithium or iodine levels are low, useful supplements to support healthy levels include lithium oratate and iodoral. A suggested starting dose is ¼ of capsule/tablet each daily. High levels of ammonia may also tend to deplete manganese levels. Manganese is also important for dopamine synthesis. It is important to monitor the level of manganese and to support if necessary.

A further result of the CBS C699T and CBS A360A mutations is that there may be high levels of sulfur groups on urine tests. Individuals with this mutation also tend to have more difficulties with sulfur containing compounds. This would include garlic, broccoli, glutathione, and even DMPS and DMSA. Once the body is supported nutritionally to address the CBS mutation these individuals are in a better position to be able to use sulfur containing compounds including glutathione.

CBS up regulations can also put some strain on the urea cycle. The availability of BH4 helps to determine whether nitric oxide, peroxy nitrite or super oxide is formed as a function of the urea cycle. Two molecules of BH4 are required for formation of nitric oxide; one molecule of BH4 leads to the formation of peroxy nitrite and the absence of BH4 leads to super oxide formation. The BH4 acts in concert with the NOS enzyme in the urea cycle to produce these end products. There is some literature to suggest that omega 3 EFAs may limit the activity of NOS. As with most other supplements this suggests that moderation is the best approach. The use of an EFA (Essential Fatty Acids) mixture that has omega 3:6:9 every other day, alternating it with a source of omega 3 fatty acids such as DHA should help to strike a reasonable balance in individuals with NOS mutations. For those individuals who do not have NOS mutations, the daily use of an omega 3 mixture in addition to the daily use of a separate source of omega 3s should be fine. In this way the body is supported for optimal membrane fluidity yet at the same time is limiting any negative effects of too much omega 3 on the NOS enzyme. A lower protein diet and the use of Stress Foundation Formula RNA once or twice daily will also help to take some of the strain off of the urea cycle. A strain on the urea cycle due to inefficient NOS activity can lead to elevated levels of ammonia that can exacerbate the ammonia problem as a result of the CBS C699T and CBS A360A mutations and lead to further drains on the already limited stores of BH4.

Preliminary collaborative research is ongoing with a group of doctors in Japan, looking at the use of prescription BH4 to help to compensate for MTHFR A1298C and CBS C699T+ mutations. The initial results in this area are encouraging. Low daily doses of BH4 (1.25 mg) initially appear to stimulate detoxification over the first several weeks of use. After this initial detoxification effect the BH4 appears to have a very positive impact on language for individuals with CBS C699T+ mutations.

- **COMT V158M and VDR/Taq Support**

The composite of the COMT V158M status along with the VDR Taq status help to define the amount of methyl donors that are included in the supplement plan. COMT is the enzyme that helps to inactivate dopamine, doing so by transferring methyl groups. Those who are COMT V158M + have enzymes that are less active meaning that they inactivate dopamine to a lesser extent. While the VDR/Taq SNP does not affect COMT activity directly it does affect overall dopamine levels. Looking at both the VDR/Taq and COMT V158 can give you an overall sense of the dopamine levels in the system based on nutrigenomics.

VDR /Taq - - represents the norm and has been reported to be associated with higher levels of dopamine. VDR /Taq + + represents changes in the gene such that the dopamine levels are reduced. Obviously there are a huge number of combinations and permutations of just these four SNPs that will lead to a wide range of levels of dopamine and rates of dopamine breakdown.

Individuals who are COMT V158M + + VDR Taq - - would tend to have the highest overall dopamine levels but also be the most susceptible to mood swings due to dopamine highs and low. This is because high dopamine levels can feedback and inhibit dopamine synthesis. Those who break down dopamine more slowly will tend to accumulate higher levels of dopamine. This is compounded by the presence of VCD Bsm/Taq - - status. The high level dopamine inhibits new synthesis such that the dopamine levels can fall until it reaches a point where the inhibition is relieved and new synthesis occurs.

Individuals who are COMT V158M - - VDR Bsm/Taq + + would tend to have the lowest dopamine levels yet their levels would tend to be more constant and may be related to more of an even temperament. Those who are COMT V158M –

and VDR Taq + may want to consider the use of additional methyl donors such as curcumin, melatonin, L-Theanine, ZEN, and MSM (not for those with CBS up regulations) in addition to the specific methyl donors SAMe and methyl B12. Also the use of small amounts of the Mood D Formula RNA, Attention Formula RNA and Mood Focus Formula RNA may be helpful to support healthy dopamine levels. In addition to the Focus Formula RNA and Mood D Formula RNA consider supplementing with quercetin. This can help to support healthy dopamine levels and also may help to limit allergic reactions in the body. Consider starting with 1/2 quercetin per day. Ginkgo Biloba has been reported to help to increase dopamine uptake; again the suggested starting point is ½ Ginkgo Biloba per day. There is also a natural source of dopamine that is available that is an extract from Mucuna Pruriens (Dopa 400). Those with lower dopamine levels could consider a very small sprinkle of this product however large doses are not suggested. If mood swings occur as a result of the supplements to support dopamine levels then decrease the dopamine supplements to half their initial dose.
As already mentioned, those who are COMT V158M - and VDR Taq + may be in a better position to tolerate supplements that contain methyl donors. L-Carnitine, CoQ10 and Idebenone all contain methyl groups and are supplements that are used for mitochondrial support. However, to aid in the detoxification process as well as to support mitochondrial energy it is beneficial for individuals of ***all*** COMT V158M an VDR/Taq types to use a mitochondrial support cocktail. This may mean that some individuals need to work more slowly to layer in mitochondrial support than others or to rotate the use of these supplements. This cocktail consists of L-Carnitine, ATP, CoQ10, Idebenone, NADH and low dose Muscle support formula. (Decreased mitochondrial energy can lead to fatigue, low muscle tone, muscle weakness as well as fine and gross motor issues.) ATP and NADH can be used on a daily basis.

Those who are COMT V158M + or VDR Taq – may want to begin by rotating these methyl containing supplements rather than using them on a daily basis. Alternatively those who have a lower tolerance for methyl donors may want to start by using only ½ of each of these supplements and then gradually increasing the dosages. By supporting the mitochondria with these supplements it should help to aid in energy production and the detoxification process. The mitochondrial cocktail can be added after the methylation support so that you are not adding too many supplements that stimulate detoxification at the same time. For those who have more severe muscle weakness and fatigue issues, you can look at supporting the mitochondria even before methylation cycle support if you desire.

The situation with Fok is also 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 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 will use the tt or TT designation to denote VDR Taq and FF and ff for Fok. Those who are tt should consider limited methyl donors. Those who are TT tend to have a greater tolerance for i.e. methylB12. Again, the bottom line is that I do feel 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.

In addition to its role in mitochondrial support, increased levels of NAD have also been shown to slow degeneration of axons in animal models of neurodegenerative disease and peripheral neuropathies. NAD levels were found to decrease in degenerating axons and increasing the level of NAD and/or nicotinamide was able to offer protection. NADH is also helpful for chronic bacterial infection and also for individuals with glucose 6 phosphate dehydrogenase deficiencies. A

deficiency of this enzyme creates problems with recycling glutathione. The use of NADH can help to reduce any oxidized glutathione and so the use of NADH may be useful in part to compensate for decreased G6PDH activity. On the other hand sulfur donors can decrease the activity of this enzyme, even if there is no mutation present. This fact is known and characterized. If you have one of the many mutations that lead to decreased activity of this enzyme then sulfur excess will be more of an issue. Deficiencies in the G6PDH enzyme cause the RBCs to be more fragile and to rupture easily leading to anemia. A G6PDH deficiency could create issues with sulfur donors and may cause problems with the use of DHEA or sulfur based chelating agents in any form including transdermal forms; potential symptoms of a sulfur toxicity problem can include broken capillaries, excessive bruising and bleeding, nose bleeds and problems with sugar regulation as well as decreased levels of 5 carbon sugars in the body. Where RBCs have a half life of 120 days in the body, it can take several months for the excess sulfur to build to a point where they have a cumulative effect on the G6PDH levels in the RBCs. It is especially important for individuals using sulfur based products to watch for signs of sulfur toxicity that manifest over the course of several months, such as broken capillaries, increased bruising, or decreased kidney function. If you do see any of these symptoms you may want to consider taking a break from the use of sulfur based products. The addition of NADH should be helpful for potential problems with G6PDH. When the G6PDH enzyme is not functioning properly, it will lead to higher levels of free glucose which can lead to bursts of insulin. This can in turn create further inflammation in the body. The use of thyroid supplementation and adrenal supplementation, alternative sources of 5 carbon sugars such as ribose and the The Right C form of vitamin C with ribose may also help to support decreased levels of G6PDH.

By supporting the mitochondria with NADH, as well as the rest of the mitochondrial cocktail it should help the body to have the necessary energy for detoxification and also may help to compensate for any mutations or deletions in SOD or in the glutathione pathway.

It may also be worth considering nutritional support for the Krebs cycle in the body. The Krebs cycle (also known as the TCA cycle) is responsible for helping to generate energy via reactions that take place in the mitochondria. The Krebs cycle is tied to our complete methylation cycle diagram via fumarate and aspartate that are part of the urea cycle. Fumarate and aspartate also a key intermediates of the Krebs cycle. Low levels of fumarate as a result of excess ammonia, OTC mutations, or NOS mutations may have a negative impact on the Krebs cycle. It is possible to supplement the Krebs cycle directly with L-Carnitine fumarate to help to compensate for low fumarate due to urea cycle issues. It is also worth considering additional Krebs cycle support based on the levels of Krebs cycle intermediates on an organic acid test. As already mentioned, it is possible to supplement with fumarate individually as well as to use forms of vitamin E succinate as a means to supplement low levels of succinate. The conversion of methylmalonyl Co A to succinyl CoA requires B12. Individuals with mutations in MTR and MTRR may show low levels of succinate due to decreased levels of B12. In addition to supporting for the MTR and MTRR mutations, it may be useful to also supplement directly with Vitamin E succinate to take some of the strain off of the need to B12 and to support the Krebs cycle directly with this intermediate. Malic acid is often used to chelate aluminum; however it will also support healthy levels of malate in the Krebs cycle. Magnesium citrate can serve as a source of magnesium supplementation as well as a source of citrate for the Kreb's cycle.

More general overall Krebs cycle support can include nutrients and supplements entitled "Krebs cycle intermediates" (provided they do not include glutamate, aspartate or their derivatives), such as zinc in a complex with Krebs cycle intermediates. Again, testing to determine the level of various Krebs cycle intermediates should be done before deciding on which supplements to utilize.

Difficulty in getting around the entire Krebs cycle can be due to lack of ATP, NADH or riboflavin. If you think of the Kreb's cycle as a clock and find that you are getting stuck at I,e, 6:00 or 8:00 you should consider the use of ATP, NADH and low dose riboflavin. By looking at the levels of the Krebs intermediates and placing the values at the "times" on the Kreb's "clock" it should be fairly straightforward to determine if you are not making it around the entire cycle properly and need this support.

Elevated oxalic derivatives combined with high pantothenic acid and high citric may suggest that we are not converting pyruvate as nicely as possible and are therefore having problems entering "the clock".

This can lead to a build up of oxalic derivatives and an increase in citric as pyruvate is the link between oxalic and citric. This may be related to some issues with glucose 6PDH levels and NADH levels that may have been affected by high sulfur detoxification and/or a CBS up regulation. Excess sulfur that is generated via this pathway may be inhibiting glucose 6 PDH and this is one possible explanation if you are a bit light in the conversion of pyruvate into the Krebs cycle. In these cases I would suggest that you consider the use of NADH.

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

Lack of B12 can also have a significant effect on the Krebs cycle. In particular, intermediates in the later part of the cycle (11:00 and 12:00 o'clock) such as oxalate and fumarate have been reported to increase with a lack of B12. Conversely, intermediates in the beginning of the cycle (1:00, 2:00, 3:00 o'clock) can build up from excess aluminum in the system. This may be a particular issue for those who are female, have MTHFR A1298C mutations, ACAT mutations and/or chronic bacteria in their systems. I have observed that extreme muscle weakness had been alleviated with aluminum excretion from the body and this would also fit with the potential effects of aluminum on the Krebs cycle. Individuals with higher levels of the intermediates in the early portion of the Krebs cycle may want to focus on layering in the aluminum support supplements and mitochondrial cocktail earlier in their supplement program.

- **MTR + , MTRR+**

If your nutrigenomic profile shows a mutation in the methionine synthase gene (MTR) or in the in the methionine synthase reductase gene (MTRR) you may want to focus heavily on B12 support. The methionine synthase mutation (MTR) is an up regulation mutation that enhances the activity of the enzyme. This can cause the enzyme to *use up methyl B12 at an even faster rate than normal*. The function of methionine synthase reductase gene (MTRR) is to *regenerate* B12 for MTR to utilize.

What both of these mutations can mean in practical terms is that you may be deficient in methyl B12. Depending on your COMT V158 M and VDR Bsm/Taq status you may want to focus on either hydroxycobalamin (Hydroxy)B12 or methyl B12 for support. It has been my experience that those who are COMT V158M + and VDR Taq – tend to have lower tolerance for methyl donors including methyl B12. Also adults, regardless of their COMT V158M/VDR Taq status seem to have more limited tolerance for the level of detox triggered by methyl B12. Those who are MTR + and MTRR + should look at high dose B12 support in my opinion. The balance of methyl to hydroxycobalamin B12 can be a personal decision based on COMT V158M/VDR Taq status as well as your own personal tolerance for B12 support. In addition to increasing doses of either methyl or hydroxycobalamin B12, the use of lower doses of cyano and adenosyl B12 (Dibencozide) with vitamin E succinate is also suggested. Supplementation can start with one chewable methyl B12 (5mg) or hydroxyl (1 or 2mg) daily. This can gradually be increased to two, three or more hydroxyl or methyl B12 per day if you will tolerate it. If mood swings occur, then decrease the dose of B12 back down to a more comfortable level. Literature suggests that oral B12 is as effective as injected B12; however as an alternative you can consider B12 injections. If you decide to use B12 injections it is preferable to use plain methyl B12 (no folinic or NAC) or plain hydroxyl B12 injections. If you choose to use B12 injections it may be worth considering the addition of the chewable B12 on the injections "off days". If you choose to use injections you can start with injections once a week and gradually increase to injections three times per week. This can be a very gradual process that is dictated by what you are able to tolerate; again using chewable B12 on the off days. If you decide to simply use the chewable methyl B12 this is an acceptable alternative. You may also want to add sublingual cyano B12 (once a day) to help to support your eyes. There is also a new nasal B12 that is available. I do not think that solely using the nasal form is the answer. I think it is important to allow for some B12 to be absorbed through the gut with the help of Intrinsic Factor. In addition the use of oral B12 sprays (available as hydroxyl or methyl), topical B12 cream, B12 gum and the B12 patch are other means by which to support B12 in the body. I like to see multiple routes and forms of B12 used until I feel that the system has been saturated with B12 (see discussion of cobalt levels below).

There is a second pathway to the formation of methionine through the BHMT enzyme that will bypass this mutation in the methionine synthase gene. This pathway uses phosphatidyl serine and /or TMG as donors for the reaction. It is wise to consider adding PS and a small amount of TMG to help to drive this reaction. While DMG works well to support language, it may be best to wait to add any DMG until this pathway is supplemented properly, as the DMG may be inhibiting this BHMT reaction to methionine. Supplementation for this part of the pathway also uses a low dose of TMG, choline and plain methionine. The Neurological Health Formula (General Vitamin) is acceptable as a source for TMG, choline and methionine as well as the other general nutrients contained in it (1 in the morning and another 1 in the afternoon). In addition, phosphatidyl serine should also be added to help to support the "back door" reaction from homocysteine to methionine via the BHMT enzyme. Phosphatidyl serine is available as plain PS/PE/PC (Phosphatidyl Serine Complex) gel caps as well as a chewable form with DMAE (Pedi-Active). DMAE contains methyl groups so this is an ideal form for individuals who need extra methyl groups based on their COMT and VDR test results. Therefore if you will tolerate it, you should consider the use of one or more phosphatidyl serine/PE/PC gel caps as well as one of the chewable Pedi-Active PS with DMAE daily. This will help to support the alternative pathway that can aid in bypassing mutations in the MTR and MTRR genes.

Again, as with the methyl B12, if you find that this is more methyl groups than you can tolerate without causing mood swings, then eliminate the use of the Pedi-Active containing the DMAE.

As the level of B12 becomes more in balance following appropriate supplementation to address the methylation cycle mutation, it can also help in balancing glutamate and GABA levels. In addition, GABA can be added directly. Those who are COMT V158M - - should also be able to tolerate, and benefit from ZEN, which contains theanine in addition to GABA, as theanine has methyl groups. There are several other supplements that are very useful for balancing glutamate and GABA; these include taurine, pycnogenol and grape seed extract. These three are included in the general vitamin; however you may want to consider adding in additional amounts of pycnogenol, grape seed extract and taurine (except for no additional taurine for those with a CBS up regulations and high taurine) as needed based on behavior especially as there are only very low doses of these in the general vitamin. GABA levels are related to language, as well as to anxiety levels, particularly anxiety in response to low blood sugar.

Lead inhibits a critical enzyme in the pathway for heme synthesis. A block in this pathway creates a build up of an intermediate that competes with GABA. Reduced GABA activity can cause auditory processing issues as well as language problems, and anxiety. In addition, inhibition of this pathway by lead can cause anemia, as well as the inability to make groups that are needed for B12 synthesis. A lack of these groups will exacerbate mutations in methionine synthase and methionine synthase reductase. This again points to the need for added B12 for individuals with mutations in this portion of the methylation cycle as well as the use of supplements to address lead toxicity in the body. The use of weekly baths or soap which contains EDTA should help to address lead toxicity in a very gentle manner that is suitable to most systems. It is also valuable to consider the use of EDTA capsules and/or the use of EDTA chewing gum.

Once the methylation cycle is supplemented properly you may begin to see an increased level of detoxification. Generally there will be a “honeymoon” period followed by a regression in behaviors as the creatinine starts to climb. In order to monitor this and to understand changes in behavior that may occur as a result of this detoxification, it is a good idea to take spot urine samples and run urine toxic metal tests. It may seem like a supplement is non ideal for an individual. However, it is difficult to tell the difference between a negative reaction to a supplement and the behavioral impact of detoxification or a mood swing due to dopamine fluxes as the methylation pathway is supplemented properly; that is why the use of regular urine toxic metal tests is so critical. The urine samples will help to separate the effects of methylation support on detoxification from supplements that do not agree with an individual.

What I look for in terms of B12 support is to continue to supplement with either hydroxyl or methyl B12 until we see a cobalt levels on a UEE reach a black line across the page. At this point I like to stay at the level of B12 support that was needed to reach this point and be certain that we have additional support in place to help with oxidized species, such as the use of trehalose, spirulina, quercetin, riboflavin, NADH, ATP amongst others. Once the cobalt levels drop back to baseline, ***while supplementing at the same high concentrations*** of B12, this is the point where we often start to see major increases in excretion. It is important to follow this process with regular UEE/UTM testing and to work in conjunction with your doctor on the detoxification process.

Individuals should also be supporting the rest of the methylation pathway with ¼ FolaPro,¼ Intrinsic B12, ½ to 1 nucleotides, ¼ dropper methylation support RNA, SAMe if it is tolerated as well as appropriate support for any CBS up regulations and for the BHMT reaction described above.

- **MTHFR C677T +**

While I find this to be the less severe mutation from the standpoint of autism, it does impact the ability of the body to convert homocysteine to methionine. C677T mutations in the MTHFR gene can therefore lead to increased levels of homocysteine if the body is not supplemented properly to address this mutation. High levels of homocysteine have been mentioned in association with heart disease, Alzheimer’s disease as well as a range of inflammatory conditions. Homocysteine also serves a regulatory function in the body. Particularly thick blood can also be associated with vascular inflammation and elevated homocysteine.

Conditions of high homocysteine favor the accumulation of S adenosyl homocysteine (SAH) in the body. SAH inhibits the activity of several enzymes in the methylation pathway including the inhibition of COMT. While this may offer certain advantages in terms of increasing dopamine levels for individuals who are COMT V158M - -, this inhibition of COMT may create mood swings for COMT V158M + + individuals.

SAH also inhibits enzymes that transfer methyl groups to DNA, RNA and proteins. High levels of homocysteine due to primary mutations in the methylation pathway (i.e. MTHFR C677T) may create secondary problems in this pathway due to inhibition of DNA methylation. Support with appropriate supplementation to address all aspects of the methylation pathway should help to alleviate these effects. Because the C677T mutation in the MTHFR is a mutation in the forward reaction of this enzyme it means that the body is less able to make 5 methyl folate and requires supplementation with this form of folate. For this reason I do not suggest the use of very high doses of plain folate or high doses of folinic. The various forms of folates are able to compete with each other for transport into the body. I feel that it is advisable to look at low doses of several forms of folate to bypass the effects of the MTHFR C677T mutation. The use of FolaPro as a source of 5 methyl THF and Intrinsic B12 as the source of additional 5 methyl THF as well as the source of 5 formyl THF (folinic) and as the source of plain folate is what I recommend.

Following appropriate supplementation to address the MTHFR C677T mutation as well as any other mutations in the methylation cycle there will generally be a "honeymoon" period followed by a regression in behaviors as the creatinine starts to climb. However, this honeymoon period may be as short as a day for individuals with a C677T mutation, combined with methionine synthase and methionine synthase reductase mutations. This combination of mutations is in such a pivotal location in the methylation cycle, that as soon as you begin to supplement properly, you may see an almost immediate effect on detoxification as this pathway is rapidly unblocked. It may be visualized as if you are suddenly opening the dike on a dam. In order to monitor this and to understand changes in behavior that may occur as a result of this detoxification, you should run spot urine toxic metal tests. It may seem like a supplement is non ideal for an individual. However, it is difficult to tell the difference between a negative reaction to a supplement and the behavioral impact of detoxification or a mood swing due to dopamine fluxes as the methylation pathway is supplemented properly. That is why the regular urine samples are so critical and why it is important, as always to work in conjunction with your doctor.

- **MTHFR A1298C +**

If your nutrigenomics test shows an A1298C mutation in the MTHFR gene you may want to focus on BH4 support as well as aluminum excretion and the gut program. The A1298C mutation has been mapped to the SAMe regulatory region of the gene. Mutations in the A1298C do not lead to increased levels of homocysteine; until now it has been felt that this mutation may not be of serious consequence. Literature suggests that the MTHFR enzyme can drive the reverse reaction leading to formation of BH4. I believe that the A1289C mutation is associated with a defect in this reverse reaction leading to the formation of BH4. The A1298C mutation would then be associated with an inability to convert BH2 to BH4 and may cause exceedingly low BH4 levels. Since aluminum can also have a negative impact on BH4 levels I feel that it is important to stress aluminum excretion for those who have MTHFR A1298C mutations. You may also notice imbalances on a MAP or OAT test that indicate blocks in the early portion of the Krebs cycle due to aluminum toxicity. Where I believe that aluminum retention in the body is related to chronic bacterial loads, and also that MTHFR A1298C mutations can limit the body's ability to address bacterial infection, I do think it is important for individuals with these mutations to also focus on the gut program, running a CSA and supplementing to help with chronic bacterial issues.

Lack of BH4 in the body can in turn affect dopamine levels as well as the levels of serotonin and urea cycle function. The COMT and VDR Bsm/Taq status may play a role in affecting overall BH4 levels as any needed synthesis of dopamine to replenish storage of dopamine will require BH4. Individuals who are COMT V158M + + or VDR Bsm/Taq - - may have an advantage in this area and the COMT V158M + + and VDR Bsm/Taq status may help to compensate to a certain extent for the effect of the MTHFR A1298C mutation.

Low levels of BH4 have been associated with hypertension and arteriosclerosis, as well as more severe parasitic infections. (This situation may be exacerbated by the finding that parasitic infections may themselves deplete B12 in the body). Lack of BH4 can also allow for mast cell degranulation which can lead to increased levels of histamine. Symptoms of histamine release can include red ears and other hypersensitivity reactions. Serotonin synthesis as well as ammonia detoxification also require BH4. Factors that lead to more ammonia, such as high protein diets, generate more ammonia that needs to be detoxified. Elevated levels of ammonia are sufficient to cause flapping and other over stimulatory behaviors. Excess ammonia in the gut may alter the local pH and aggravate imbalances in microbial flora. Each molecule of ammonia requires two molecules of BH4 for ideal detoxification. It is clear to see how several of these factors may act together to impact ammonia detoxification as well as optimal BH4 levels for neurotransmitter synthesis. Keeping the ammonia levels under control is of paramount importance for overall health and wellness, especially for an individual with an MTHFR A1298C mutation as any excess ammonia generated can drain stores of BH4. This can impact upon serotonin levels and to a certain extent cause fluxes in dopamine (which translates into mood swings). Also helping to restore adequate levels of BH4 should aid in serotonin synthesis, maintaining dopamine levels in a more stable manner as well as ammonia detoxification.

As already mentioned, MTHFR A1298C mutations can lead to decreased levels of BH4. The recycling of BH2 to BH4 is also inhibited by aluminum. From this standpoint it is important for those who are MTHFR A1298C + to address aluminum and bacterial detoxification in system at some point. CSA tests give an indication of chronic bacterial issues, and based on the literature as well as my personal experience, bacteria can harbor aluminum. Aluminum inhibits BH4 synthesis. Since MTHFR A1298C mutations can also affect BH4 levels, you would be best served to eliminate the aluminum from the system so that you will have removed that impediment to appropriate BH4 recycling. This does not have to be done right away, but should be dealt with once detoxification from methylation and mitochondrial support has slowed down. BIoThyro or BioOrgan, in conjunction with OraLiv and NADH can be used to support natural BH4 levels. The use of horsetail grass, malic acid and EDTA can be considered to help with aluminum excretion. The use of low dose CCK support is also suggested. I have found that CCK may help to trigger bacterial detoxification. The starting dose for CCK (Resist Fat Apex Lean) as a supplement is ¼ to 1/8 per day in conjunction with CCK Support RNA. Over time the dose of CCK can be increased to 1 tablet per day in divided doses. Adding in the gut/microbial program discussed below will help to support bacterial detoxification, and to allow for aluminum excretion along with helping to balance the gut flora.

- **Mao A**

The mao A gene, codes for the enzyme involved in serotonin breakdown. Individuals with a mao A + status may show decreased enzyme activity such that mao A is less effective in degrading serotonin. Similar to the situation that is observed with individuals who are COMT V158M +, those with maoA ++ status may also be subject to mood swings due to serotonin cycling from high to low levels. In some cases I have observed that aggressive behaviors may in part be associated with maoA + + status and the use of the Behavior formula may be helpful in these cases. In addition, as discussed in the section concerning the gut and bacterial issues, chronic infection in the body can deplete storage of trypophan and this may be reflected in higher levels of 5 hydroxy indole acetic acid (5HIAA) on organic acid tests and urine amino acid tests as well as increased OCD type behaviors. Lack of BH4 due to aluminum toxicity, increased levels of ammonia or MTHFR A1298C mutations can also impact on serotonin levels. The use of frequent low doses of Mood S Formula RNA and 5HTP may be helpful to maintain healthy balanced serotonin due to maoA + status or due to some of these other conditions.

Recall that similar to the situation with the ACE deletion, that the maoA gene is not inherited via standard Mendelian genetics. The maoA gene “travels” with the X chromosome and is considered a dependent trait. Since the X chromosome in males can only come from the mother, this means that the father’s maoA status does not play a role in the son’s maoA results. For females, since one X chromosome comes from each parent, the genetics will tend to reflect both parents with respect to the maoA SNP.

- **SHMT Support**

The SHMT mutation has been well characterized by Dr.Patrick Stover. Based on his work, I feel that the net effect of the SHMT mutations is to shift the focus of the methylation cycle away from the long route, and toward the formulation of thymidine. For this reason we look at supplementing with nucleotides to take some of the pressure away from the need for thymidine synthesis. In addition, SHMT is regulated by iron in the system as well as by the level of 5 formylTHF. The use of lactoferrin and low doses of 5 formyl THF are again designed to help shift the focus of the methylation cycle back to the long route, and the short cut through the cycle, rather than diverting resources away from these important aspects of the methylation cycle.

- **SUOX and Sulfite Toxicity**

The presence of an SUOX mutation on the nutrigenomic panel is very rare. The SUOX refers to the enzyme that helps to detoxify sulfites to sulfates. Imbalances in this enzyme activity can lead to increased amounts of toxic sulfur byproducts. In addition, this enzyme uses molybdenum for activity as a cofactor. As a result of the SUOX not working properly, it can lead to depletions in molybdenum.

Molybdenum is also needed to keep the zinc/copper ratio in balance. Without adequate molybdenum the copper levels can rise too high relative to zinc and this can cause problems in the body. Excess copper can cause fatigue, depression, insomnia, rashes, and adrenal burnout, among a variety of other symptoms. For individuals with SUOX mutations, as well as those who are CBS C699T+, I seriously suggest frequent regular urine essential element tests as well as urine toxic metal tests to keep a close eye on the essential minerals in your system. This is important during detoxification of heavy metals, but it is also important due to the potential effect of the SUOX mutation on zinc and copper levels. In my opinion, the best way to address the SUOX mutation is to limit the use of sulfur based compounds. I would also pay careful attention to sulfites in foods as your body will have difficulty converting sulfites to the less toxic sulfate form. Sulfites may also be playing a role in the extreme acid reflux that individuals with the SUOX + - status appear to experience. Dried

fruits and aged meats are often sources of sulfites. Certain brands of tuna contain sulfites, and salad bars often use sulfites to prevent the lettuce from turning brown.

Decreased molybdenum levels as a result of SUOX mutations, increased CBS activity or increased ingestion/use of sulfur containing compounds can lead to depletions in molybdenum. The secondary effects of low molybdenum include the inability to detoxify sulfites as well as decreased xanthine oxidase and aldehyde oxidase activity. Higher levels of xanthine oxidase are found in homogenized milk; dairy intolerances may be seen in individuals who have the SUOX + - status (or those with CBS + due to increased burden on the SUOX). Aldehyde oxidase is needed to detoxify aldehydes, including acetaldehyde. Acetaldehyde is a fungal waste product that is generated by Candida. Aldehydes are also found in perfumes, foods, as well as environmental toxins. Food sources of aldehydes include vanilla, cinnamon (including cinnamon flavored toothpaste), cumin and tarragon and in the breakdown process of alcoholic beverages. As already discussed, molybdenum acts as a cofactor for the enzyme aldehyde oxidase. Molybdenum levels should be followed carefully with urine essential mineral tests. Molybdenum can be supplemented with mineral sources or through the intake of foods that are high in molybdenum. Food sources of molybdenum include Barley, Beef Kidney, Beef Liver, Buckwheat, Hot Cocoa, Eggs, Legumes, Yams, Oat Flakes, Potatoes, Rye Bread, Spinach, Sunflower Seeds, Wheat Germ, Green Leafy Vegetables. Individuals with SUOX + - status ,CBS up regulations or high ingestion of sulfur compounds may demonstrate higher food and environmental sensitivities which stem in part from a lack of aldehyde oxidase activity that is secondary to decreased molybdenum in their systems.

Several of the individuals that have presented with a SUOX + - status have also complained of severe acid reflux that seems to be non responsive (or showing only limited responsiveness) to more classic medications for Gastroesophageal reflux (GER). Standard medications for acid reflux tend to be targeted at the mechanism that triggers excess acid in the stomach (histamine 2 blockers). It is possible that for individuals with SUOX issues, that the root of the problem is the excess sulfites creating allergic/asthmatic type reactions that have a secondary effect on acid reflux. Gastroesophageal reflux (GER) occurs commonly in patients with asthma and a relationship between asthma and acid reflux had been noted for quite some time It is uncertain whether the asthma causes the acid reflux, or if the converse is true. High sulfites are known triggers for asthma. There are some indications that the sequence of events that occur in asthma may lead to the excess acid production. Ordinarily we think of histamine reactions as allergic reactions; however it is important to realize that it is over activity by histamine receptors that is tied to the excess acid production observed in GERD(Gastroesophageal ReFlux). According to Pneumological Aspects of Gastroesophageal Reflux (edited by Dal Negro and Allegra). "*Gastroesophageal reflux (GER) refers to symptoms and events that result from abnormal regurgitation of gastric contents into the esophagus. Respiratory diseases, in particular bronchial asthma, can be exacerbated by multiple triggers, including GER. The relationship between the occurrence of gastroesophageal disorders and changes in respiratory function has been known for over a century, but the mechanism by which esophageal acid regurgitation can produce respiratory symptoms is still debated. The reasons for these concurrent pathological events are also not fully understood.* ***Determining, for instance, whether reflux itself initiates or exacerbates asthma, or whether asthma or its treatment primarily causes GER is a matter of current investigation."***

Obviously this work suggests that it is worth considering that acid reflux seen in individuals with SUOX mutations or with CBS up regulations may be related to the excess sulfites in their systems. Maintaining adequate levels of molybdenum, limiting sulfur donors, and the use of Respiratory Support Formula RNA as well as the Stomach pH Balancing Formula RNA, Stress Foundation Formula RNA and may be beneficial in helping to balance the acid reflux. Quercetin can be used to limit mast cell degranulation for those individuals who are COMT - - or COMT + -. In addition, Petadulex (butterbur) may be helpful in balancing allergic/histamine reactions.

Urine essential element testing is also important to track magnesium levels. Adequate magnesium has been shown to be helpful in addressing asthma and may therefore be of benefit for those with high levels of sulfites in their system. Magnesium given IV was able to prevent hospitalization and reverse symptoms of asthma attacks in spite of the fact that the children in the study were unresponsive to three prior doses of bronchodilators. (Ann Emerg Med. 2000;36:181-190.). This serves to emphasize the importance of keeping a close eye on both essential as well as toxic minerals on a regular basis.

The potential effect of excess sulfites on acid reflux is not to minimize the effect that heavy metal toxicity and chronic viral infection can have on potential acid reflux. Acid reflux may also tie in directly with chronic viral infection in the body. Cimetidine (Tagament), an OTC medication for heartburn, has been demonstrated to have efficacy against herpes virus (LEF March 2001). This would suggest that chronic viral infection may also play a role in acid reflux. The use of OTC heartburn medication may appear to aggravate the condition, while in actuality it may be acting to aid in viral detoxification

and the concomitant release of metals from the system. The use of urine toxic metals tests are useful in determining if this is indeed the case.

Finally support with high level B12 has been reported to make a positive difference for those with sulfite sensitivity. Improvements in asthma have also been reported with high dose B12 support. Lack of B12 may increase stomach acidity, actually exacerbating acid reflux which is another indirect way of saying that those with SUOX mutations, with sulfite sensitivity, or with asthma may want to consider high dose B12 support as described in the sections for MTR and MTRR, even if you do not have an MTR or MTRR mutation.

- **Ace Support (most people should take the Ace Support even if they have not been tested)**

Deletions can occur that affect the activity of the ACE (angiotensin converting enzyme). Up regulations in activity of this enzyme due to deletions can lead to higher than expected conversion of angiotensin I to angiotensin II. High levels of angiotensin II in turn increase the level of aldosterone. High levels of aldosterone lead to decreased excretion of sodium in the urine and increased excretion of potassium in the urine. This suggests that low sodium and high potassium on a urine essential element test may reflect aldosterone excess and may indicate ACE up regulations. This information can be particularly useful if the genetic information for the ACE deletion did not process properly for your genetic sample, or if you have not run a test that identifies the ACE deletion. It is then possible to use the urine essential element excretion data to get a sense of the ACE deletion. In addition, the essential element test results can be used to confirm the effect of changes to your supplement program on this mutation. Elevated excretion of potassium relative to sodium is a strong indicator for the ACE deletion in the absence of appropriate supplementation. After supplementation, urine essential element test results can be used to verify that you have had a positive, balancing effect on potassium and sodium excretion with your supplement program. In animal studies high levels of angiotensin II were correlated with increased anxiety and decreases in learning and memory. High levels of aldosterone also tend to increase the activity of AHCY.

Support for ACE mutations in this pathway can include ACE+ Mutation Support Formula RNA, Kidney Support RNA, CBS/NOS/Kidney Compound, OraAdrenal(OraAdren-80), Stress Foundation Formula RNA and Progesterone Cream (Pro-Gest Cream). BioNativus trace minerals can be used for a general mineral support.

Aldosterone can also be regarded as a stress hormone as its levels are elevated in the blood following stressful situations. Consequently, even in the absence of an ACE upregulation, situations of chronic stress can result in increased levels of aldosterone causing 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.

While the initial effect of increased aldosterone is the retention of sodium and increased secretion of potassium, over time, as the adrenals become fatigued and unable to release adequate amounts of aldosterone and/or cortisol the levels of potassium start to rise and sodium levels may begin to fall in the body. When this occurs it can result in increased retention of potassium.

In cases of imbalances in sodium and potassium excretion it is worthwhile to consider adrenal and kidney support. Also reducing stress is helpful as aldosterone is basically acting like a stress hormone.

ATP is important in maintaining the balance between sodium and potassium levels in the body. Certain toxic minerals, such as thallium are reported to have a negative effect on ATP levels. I have found that it can often be difficult to keep sodium and potassium in balance until we have adequate ATP support in place and until there has been sufficient excretion of thallium from the system.

General support for the adrenals and kidneys in the absence of specific ACE mutations includes OraKidney, OraAdrenal, Stress Foundation Formula RNA and Kidney Support RNA. Again, ATP support may be important regardless of the presence of an ACE deletion, particularly if there are high levels of toxic metals such as thallium in the system.
On a related note, licorice is often used for a number of healing purposes. It should be recognized, however, that licorice inhibits enzymes that break down aldosterone and cortisol and so its use may be non ideal for those with imbalances in these regions. The use of licorice can lead to increased levels of aldosterone. Licorice can also cause an increased craving for salt, loss of potassium and increased water intake. This may be related to its inhibition of the enzyme11 beta hydroxysteroid dehydrogenase. Grapefruit juice also inhibits the activity of this enzyme. I would suggest that individuals with imbalances in sodium and potassium excretion on UEE tests may want to avoid licorice and grapefruit juice.

Hormones, such as progesterone and estrogen are also capable of affecting the levels of aldosterone. Progesterone tends to decrease the effects of aldosterone, which would suggest that it may be beneficial for individuals who are showing negative effects of elevated aldosterone in terms of excess fluid retention or increased excretion of potassium. Conversely, estrogen appears to enhance the level of aldosterone.

Finally, please understand that with respect to the ACE gene we are looking at a deletion of that gene and not a SNP. As such it may not distribute in the same manner as single based changes and so it may not track in the same manner as SNPs when looking at familial patterns of inheritance. 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.

- **Glutathione Support**

Glutathione plays an important role in the body especially with respect to detoxification. Regardless of whether there are mutations in the GST enzyme pathway it would make sense to support healthy glutathione levels in the body as it is a factor in terms of metal accumulation in your system. Remember that one of the roles of the transsulfuration pathway is to generate glutathione and taurine. The level of cysteine that is detected by the cell, determines if that cysteine goes on to make taurine or to make glutathione. Low levels of cysteine favor glutathione synthesis. High levels of cysteine lead to the synthesis of taurine. The reason that you see such high levels of taurine with a CBS up regulation (C699+ or A360A) is that the cysteine generated is so high that the pathway is shunted toward taurine formation. Indications in animal models are that the CBS C699T represents a 40 fold increase in enzyme activity (the CBS A360A (C1080T) is not as strong of an up regulation). It is not surprising that it is often difficult to see appreciable levels of homocysteine, cysteine or cystathionine for some individuals with these CBS up regulations as there is such a rapid conversion rate ultimately to taurine. In many cases our best indication of the CBS up regulation on an amino acid test is the very high levels of the ultimate end products of taurine and ammonia.

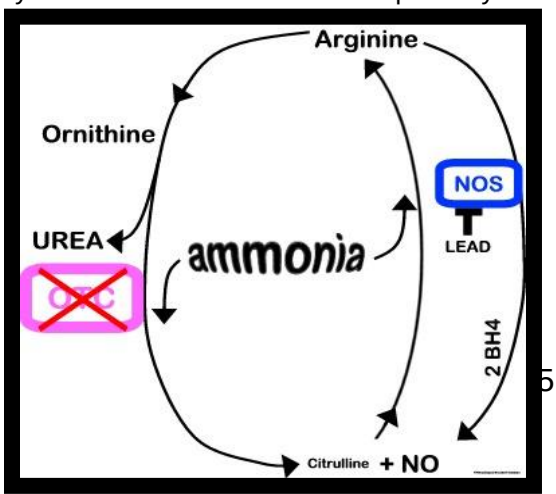
While I do not object to adding glutathione, my position is to first get this portion of the pathway in balance. To address CBS upregulations and to look at taurine levels on a UAA prior to high level glutathione support. It has been my experience that once we get the methylation cycle in better overall balance, the glutathione levels will increase naturally on their own. At that point we can look at additional glutathione supplementation, so that we are enhancing natural levels of glutathione in a system that is in balance.

Recall that glutathione is a sulfur containing compound and excessive amounts of sulfur donors can lead to decreased levels of glucose 6 phosphate dehydrogenase (G6PDH). Rather than going with the philosophy of the “more glutathione the better” it is important to temper this with an eye toward keeping glutathione supplemented but not going overboard in terms of the total number of sulfur donors in the system and keeping G6PDH in mind. Choices for glutathione supplements can include the use of topical glutathione, oral glutathione as well as IV glutathione with the addition of

NADH. The use of NADH should help to compensate for issues with glutathione recycling that can be caused by G6PDH deficiencies. NADH is also important to help keep added glutathione in the reduced form.

There are several different types of glutathione lozenges as well as a specially formulated GSH oral glutathione, an oral lipid based glutathione for enhanced transport. You can also consider using NAC (500mg per day), vitamin C with rose hips (500mg two to three times per day), vitamin E with mixed tocopherols, and selenium. These supplements can help to maintain and regenerate healthy glutathione levels without directly adding too many sulfur groups. The HHC Neurological Health Formula general vitamin includes low doses of several sulfur donors such as taurine, broccoli extract and garlic which will also be beneficial. The use of any combination of these products is suitable.

Curcumin helps to support the activity of the enzyme leading to glutathione synthesis via the transsulfuration pathway. However the use of curcumin can be a double edged sword for those with a COMT V158M + status. Curcumin is a methyl donor, and as such it may be a problem for some individuals. On the other hand, it can be useful to help promote natural glutathione synthesis.



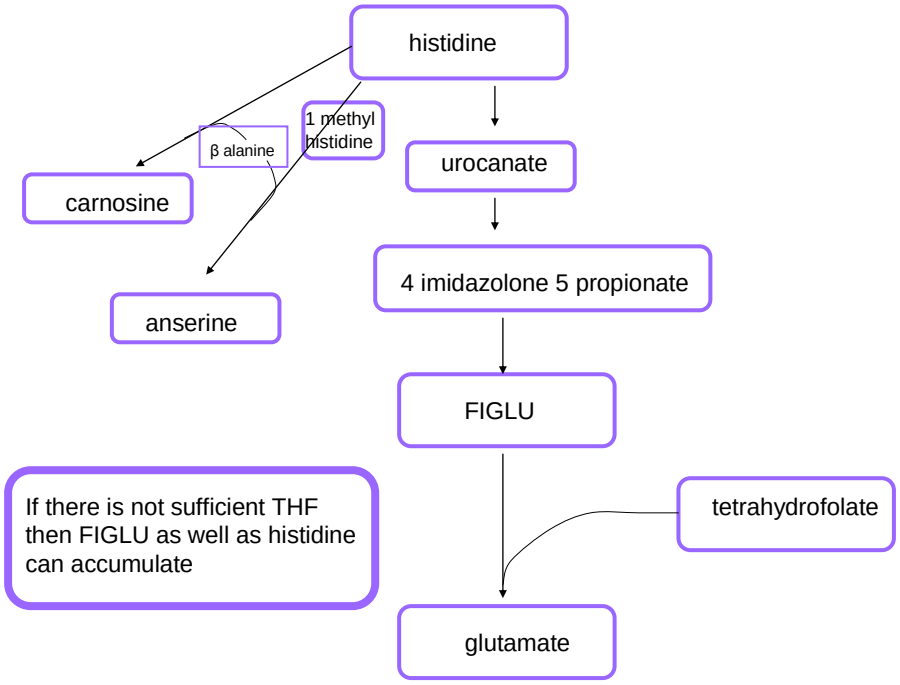
- **Urea Cycle Support**

The purpose of the urea cycle is to detoxify ammonia that is generated by the breakdown of proteins that are eaten in the diet as well as ammonia that is generated by CBS up regulations. Several of the genes in the methylation cycle have an impact on urea cycle function. The NOS enzyme plays a central role in the urea cycle as already described. This

is the reason that only low doses of EFAs are suggested for those with NOS mutations. In addition BH4 plays a role in working with NOS to safely detoxify ammonia. For this reason decreased levels of BH4 due to MTHFR A1298C mutations, aluminum due to chronic bacteria or CBS up regulations that cause excessive use of BH4 all play a role in the urea cycle. Another key enzyme in this cycle is OTC (ornithine transcarbamylase).
OTC function can be affected by the status of the methylation pathway. Methylation cycle function controls the ability of this enzyme to turn on and off. For this reason, until you have supported the methylation cycle with comprehensive support we often see decreased OTC function.
OTC enzyme "sits" between ornithine and citrulline in the urea cycle. When OTC activity is compromised you will often see low citrulline yet high ornithine on a urine AA test. Lack of OTC activity will also cause a bit of a back up in the urea cycle. This results in midrange to high levels of arginine and low levels of aspartate. Finally, this cycle also generates fumarate to be used in the Krebs cycle. The urea cycle and the Krebs cycle are linked though aspartate and fumarate. By looking at MAT/OAT tests along with urine AA test results you can see the impact of decreased OTC activity. It will generally present with low citrulline, mid range arginine, mid to high ornithine, very high fumarate, low to very low aspartate and decreased malic acid. In these cases I suggest that you consider supporting with low doses of citrulline, malic acid, BioThyro and if aspartate is particularly low then ¼ Krebs cycle intermediates. As the methylation cycle gets into better balance by addressing CBS up regulations, and support with FolaPro, Intrinsic B12, nucleotides and B12 then the OTC issue will usually resolve. If the methylation cycle function is back in balance as judged by normal range FIGLU, normal range methylmalonic acid, taurine in normal range and succinic in normal range, and these factors are still out of balance (low aspartate, low malic, high fumarate, low citrulline, high ornithine).

- **General Amino Acid Support**

As discussed above, citrulline is an amino acid that is part of the urea cycle and is involved in ammonia detoxification. I suggest that you consider the addition of low doses of citrulline if it is observed as being low on a urine amino acid test. This is suggested with the citrulline is low due to reduced OTC function as described above, or due to excessive urea cycle activity as a result of CBS up regulations. Along the same lines, other sources of amino acids that I suggest to support low overall levels of amino acids include using the Amino Care amino acid mixture. This is a general amino acid support that is available as a tablet as well as a topical lotion. I suggest only ½ tablet per day. This is a special amino acid mixture that was actually designed for cancer patients. High glutamate can be an issue for cancer too. This mixture is designed to support amino acids without increasing glutamate. I also will often suggest branched chain amino acids. The mixture I like to use includes only leucine, isoleucine and valine. The suggested starting dose is ½ capsule, provided that there is no maple syrup smell in the urine following supplementation. BCAA can also be helpful for keeping glutamate in check. If proline is very low I suggest adding ½ capsule or less. Alanine may be helpful for issues related to DPT, as discussed in the autism book; again, the suggested dose is ¼ to ½ capsule.



For those with low overall amino acids the combination of Bowel Formula 3X a day with 1 OraAdrenal seems to improve this issue tremendously. Low overall amino acids also seem to be a particular issue for those with MTRR 11 mutations and the use of 1 OraAdrenal with Bowel Formula 3X a day is recommended for those with MTRR 11 mutations as well as those with low overall amino acids on UAA tests.

Finally, if histidine, carnosine and anserine are all low, then it is worth considering histidine support. In order for the histidine to be metabolized properly, it requires a functional methylation cycle. High levels of FIGLU will be seen on an

OAT test if there is adequate histidine, yet insufficient folate to convert the FIGLU properly. Elevated FIGLU on an OAT test, indicate the need to support the methylation cycle to bypass the mutations in this pathway. The amino acid, methionine is supported directly by the Neurological Health Formula (General Vitamin). Additional support for the rest of the methionine/folate cycles discussed in this document will help to support the remainder of the pathway.

- **Gut, Sinus, Microbial Support/Thyroid Support**

It has been my experience that ACAT and SHMT issues can contribute to the gut environment in a negative manner. So as you look to get the gut back in balance I would suggest that you both address the **gut environment** as well as looking at **specific gut bugs** that may be a particular problem. I would start by focusing on ACAT and SHMT support for those who have these mutations. This can be done prior to addressing CBS issues or simultaneously. In addition, for those with ACAT and SHMT mutations it may be worth looking at the more comprehensive program designed to help with gut imbalances.

As already discussed, lack of B12 can contribute to increased acidity in the gut, which in turn can affect the balance of normal flora and non ideal gut bugs. Looking to have adequate B12 support in place is another aspect of addressing the gut environment along with specific gut bugs.

The use of vitamin C and Biotene toothpaste or mouthwash (available at your local pharmacy) may be useful in combating chronic streptococcal infection. The Biotene toothpaste, mouthwash and gum may also aid the mitochondria in detoxification and help to support SOD and glutathione mutations. Many individuals have issues with chronic streptococcal infection or chronic issues with other bacterial infections in the body. In addition chronic gut issues can indicate an underlying bacterial infection in the body.

Streptococcal infection in the gut can serve as a reservoir to reinfect the sinuses. Chronic streptococcal infection has been associated with OCD behavior as well as tics, over stimulatory behavior and perseverative speech. Streptococcal infection can also lay the groundwork for leaky gut which can relate to decreased weight gain or slower growth.

Xylitol nasal spray will help to eliminate nasal strep, reduce ear infections and has been reported to help with leaky gut, most likely by deceasing the flow of streptococci from the sinuses into the gut. Xylitol is also available as a sugar for cooking and in Biotene gum, toothpaste and mouthwash. Another tip is to add in papaya enzyme with increased doses of vitamin C. This helps to support the body to eliminate chronic sinus issues as well as the reservoir of strep in the gut. I suggest that you use as much papaya enzyme and vitamin C as your body can tolerate without causing loose stools. ImmunFactor 5 once every other day will aid the body in addressing the bacterial issues as well as the use of Microbial Support RNA on a daily basis. The supplement IP6 may help to reduce stimulatory behaviors and OCD behaviors associated with chronic streptococcal infection as will the use of benfotiamine. The use of lactoferrin is also excellent to support the body in addressing streptococcal and other bacterial issues as it helps to limit the availability of iron for the microbes. This may also be helpful in reducing elevated levels of RBCs and high hematocrit values. Many microbes require the presence of iron for growth and/or virulence.

Aside from the toxic effects of mercury on the body, aluminum and lead toxicity can cause toxicity in the body. Bacteria seem to be able to hold onto aluminum. Aluminum is known to inhibit glutamate dehydrogenase which is an enzyme that converts glutamate to alpha keto glutarate. In addition aluminum interferes with the production of BH4. Therefore the presence of aluminum may be affecting levels of serotonin as well as dopamine in the body and may be affecting BH4 levels regardless of whether there is an MTHFR A1298C mutation. Malic acid, EDTA and horsetail grass are all helpful in binding aluminum in the body. As chronic bacterial infection is addressed it should help to aid in aluminum excretion.

As already mentioned the gut may be a source or reservoir for chronic bacterial infection if it is an issue in the body. There are a number of herbs that are useful in supporting the body to address bacterial imbalances in the gut .One natural mixture that appears to work includes neem, myrrh, golden seal, cranberry, Oregon grape, barberry, uva ursi; using ½ to one whole capsule of each three times per day for one month. If a CSA test indicates that organisms are resistant to any of these natural herbs a substitution can be made such that the resistant herbs in question can be replaced in the mixture with caprylic acid or oregamax. Using a mixture of herbs such as these seven or more herbs simultaneously is less likely to lead to resistance than using single herbs to support the body in addressing microbial issues.

Cranberry is also excellent for support for the body to address E.coli and neem is supportive for parasites as well as for bacterial issues. Low levels of BH4 as a result of high aluminum in the body or as a result of mutations (MTHFR A1298C

or CBS up regulations) can lead to more severe parasitic infections. The use of Paradex is also helpful for supporting the body to address parasites.

It is also important to support normal flora. One successful strategy is to rotate the normal flora to get a good mixture and variety. Preferred sources of normal flora include suprema dophilus, Florastor, Ultra dairy support (even if you are not eating dairy this is a good source of flora), a sprinkle of Toueff, Colon Health Support and allerdophilus and IMF #7. If possible use ½ to one whole capsule of a different source of normal flora each day of the week. You can also use the Mycology Support RNA and Candex once a day, as well as the Bowel Support and Stomach pH Balancing Formula RNA to help to balance the gut. By following this plan, you create an environment where the normal flora can thrive and as a result you will help to eliminate the offending organisms. At the end of a month it is a wise idea to run a complete stool analysis (CSA) to confirm that the gut flora is in balance.

Loose stools are an issue for a number of individuals, and I do understand that the SCD (Specific Carbohydrate Diet) has made a big difference in these cases. However, if you are supplementing protein it is important to monitor ammonia levels to be certain that the body is able to dispose of the ammonia properly that are generated from the intake of high protein foods. The body uses two molecules of BH4 to detoxify one molecule of ammonia to urea. This is an expensive way to use your BH4. BH4 is also needed for dopamine and serotonin as well as language related function. Since language is a primary problem for many children, using up limited BH4 to detoxify ammonia may not be the best use of it for the body. In addition, ammonia is reported to inhibit he metabolism of butyrate, along with other short chain fatty acids. Butyrate is a nutrient used by cells that line the gut. Butyrate synthesis can be inhibited by H2S and sulfites that are generated as a result of the CBS up regulation, low molybdenum or SUOX mutations. Paradoxically, butyrate has been reported to be a potent detoxifier of ammonia. Ammonia detoxification also depletes stores of manganese that are needed for healthy dopamine levels.

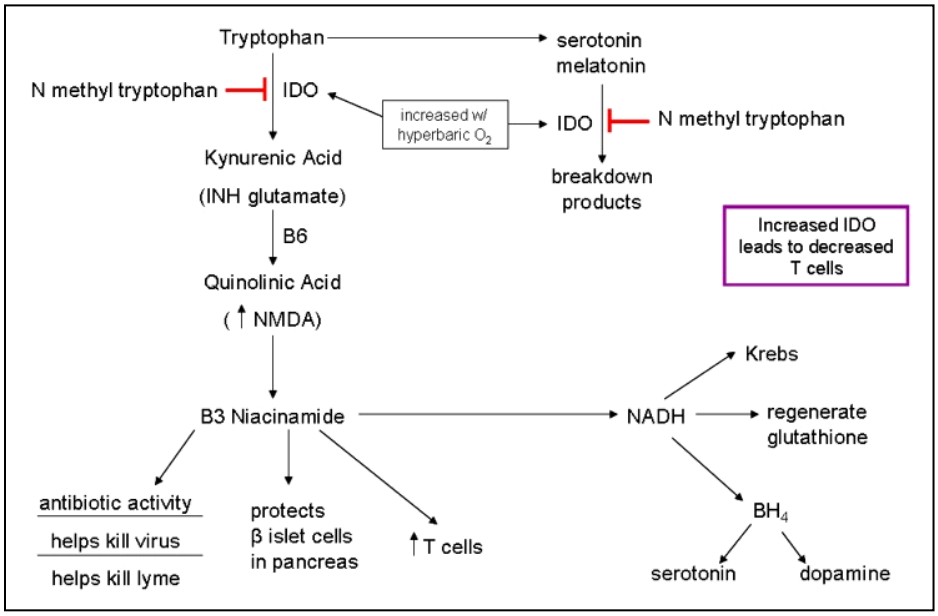
Excess stomach acid in the system can cause loose stools and severe stomach pain. Ammonia that is generated from excessive protein is alkaline. This may help to neutralize the stomach acid and would make the stools and gut pain better. However, using a high protein diet to address loose stools is not dealing with the root of the problem if it is caused by excess stomach acid. Creating high ammonia levels via diet to neutralize acids treats the symptom but not the underlying imbalance in the body. Stomach acid is triggered by histamine reacting with H2 receptors in the stomach. So a high protein diet may be increasing ammonia which is neutralizing the stomach acid and improving the gut issue. However, it is not addressing why you have excess acid in the first place nor is it considering why there may be high histamine in the system (histamine is related to methylation function). In addition it is important to evaluate ammonia levels and to consider the consequences of high ammonia. I am not suggesting that individuals abandon the SCD diet, especially as it has made a positive difference for many people. However, I would suggest a test for Helicobacter pylori as that is often a causative agent for excess stomach acid. The use of mastica gum is reported to be very helpful for addressing this organism. I would suggest ½ mastica gum, Stomach pH Balancing Formula RNA and Bowel support with meals. I would also suggest that you consider running a DDI urine amino acid test so that you can look at ammonia levels and amino acids while on the SCD diet.

On a related note other helpful tools for addressing bacterial and viral infection and supporting the body in the process include the use of Ora Triplex, Immuno Forte, Moducare and the ImmunFactors (IMF). In particular IMF 4 should be helpful for viruses related to childhood vaccines. The IMF 1, 2 and 6 should be helpful in supporting the body for herpes related viruses and I have found that the IMF 5 works nicely for support for bacterial infections. Those individuals with CBS up regulations should limit their use of IMFs to one per day due to lipid acting components in the product.

Chronic bacterial infection and its effects on tryptophan breakdown are part of the reason why I suggest only low levels of P5P for individuals with chronic bacterial issues and CBS up regulations. P5P also helps to push the CBS reaction as well as to aid in the conversion of kynurenic to quinolinic The kynurenic that is generated via the breakdown of tryptophan by bacterial infection is calming; however P5P helps to convert it to quinolinic which is excitatory as diagrammed below.

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

In animal models vitamin B2 (riboflavin) has been shown to speed the clearance of bacteria from the body and to lower mortality rates from bacterial sepsis. In addition, riboflavin is reported to be helpful in reducing inflammatory mediators. Another B vitamin, vitamin B3, is often depleted in individuals with chronic bacterial infections. You may also want to consider niacinamide (1/2 per day) as this may help to stem the breakdown of tryptophan that is often seen with bacterial infection. Kynurenate is part of the breakdown pathway for tryptophan. As the body breaks down tryptophan for this purpose it will also deplete serotonin. Lack of serotonin combined with streptococcal infection can lead to perseverative and OCD behaviors in addition to other effects. The new SNP panel looks for mutations in the mao A gene, which is the enzyme involved in serotonin breakdown.



Individuals with a mao A + status may show decreased enzyme activity such that mao A is less effective in degrading serotonin. This may mean that OCD type behaviors may be less of a problem or less noticeable, even if chronic bacterial infection is an issue. This may also be reflected in higher levels of serotonin, tryptophan or lower levels of 5 hydroxy indole acetic acid (5HIAA) on organic acid tests and urine amino acid tests.

The final breakdown product of the tryptophan pathway is niacinamide. This B vitamin has been reported to have antimicrobial effects. It may be that the body is trying to address bacterial infection by breaking down tryptophan into niacinamide to help with infection. In some cases I have not found that the use of high dose B6 or P5P is always helpful. It can actually cause more over stimulatory or OCD type behaviors. While kynurenic acid is calming for neurotransmitters, the product that kynurenines are converted to by B6 is quinolinic acid. Quinolinic acid is an excitotoxin. So if you have high kynurenine and add B6 you can generate quinolinic acid which acts as an excitotoxin and can aggravate the nervous system. Increased levels of quinolinic acid have been implicated in Alzheimer's disease as well as with respect to excitotoxin damage of nerves.

Quinolinic acid was found to be substantially elevated in patients with Borrelia burgdorferi (Lyme) infection and has been postulated to play a role in contributing to neurological and cognitive defects associated with Lyme disease.

It is of importance to try to look at why you may have elevated activity in the tryptophan breakdown pathway in the first place. Decreased methylation, increased IDO (an enzyme that is also effected by methylation and other factors), and chronic streptococcal or even B. burgdorferi (lyme) infection can lead to stimulation of this pathway.

A future consideration may be to look at addressing the possibility of chronic Lyme infection in the body. Lyme disease has been implicated in a number of neurological conditions. Cat's claw is reported to be helpful for viral issues as well as for Lyme. Artemisia (wormwood) has also shown activity against Lyme. Wormwood is a component of Paradex that was already mentioned with respect to other parasitic infections. In addition, tick support RNAs and IMF 2 should help to support the body.

Periodic thyroid tests and CSAs to assess the status of bacterial infection and it effect on thyroid function are suggested for individuals who have issues with chronic bacterial infection, sinus infections, dental issues, or a past history of ear infections.

One of the enzymes that is activated during chronic bacterial infection can also deplete tyrosine levels. The amino acid tyrosine is a precursor for both thyroid hormones as well as for dopamine synthesis. If tyrosine levels are being depleted you may be having dopamine issues in spite of the COMT and VDR Bsm/Taq status. While this may not be an issue,

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

again, this is a good time to raise potential problems so that you can be aware of them and watch for signs of these on future tests. Low thyroid function can be associated with chronic sinus infections. It is a good idea to check thyroid status particularly in individuals with chronic bacterial or sinus infections as are often found in association with a variety of neurological and cardiovascular conditions. Natural thyroid supplementation is available in the form of thyroid/tyrosine supplements. Iodine levels also affect thyroid function and there is a relationship between the methylation cycle, sulfur groups and iodine levels. Iodine levels will be impacted negatively by bromine that is used in bread. This is another reason to be vigilant with the gluten free aspect of the GF/CF diet. Lithium is concentrated in the thyroid and can inhibit iodine uptake. This is why it is important to monitor both the levels of iodine as well as lithium on essential mineral tests and supplement only as needed for low values that may occur as a result of detoxification and excretion of mercury.

If thyroid hormone levels are an issue, the use of ½ to one Iodoral per day may be of help in supporting healthy iodine levels. The use of the herb guggul may help to balance T3 and T4. After four weeks of nutritional support you should run a follow up thyroid test with your health care provider to confirm that thyroid hormone levels are in the normal range and an essential mineral test to confirm healthy iodine levels (or the use of the topical iodine test). The thyroid hormone iodination cycle is tied to glucose 6 phosphate dehydrogenase levels. G6PDH levels are affected by sulfur groups. As thyroid issues are addressed it can help to clear the chronic bacterial/sinus infections in the body.

Chronic streptococcal infection, and possibly E.coli infection can lead to a variety of inflammatory mediators as well as depleting neurotransmitters. Bacterial infection is also known to increase the levels of inflammatory mediators such as IL6 and TNF alpha. Mutations have been characterized that aid in increasing the levels IL6 or TNF alpha in the system. Elevated IL6 has been reported to inhibit the release of thyroid hormones in addition to its role in enhancing inflammation. The use of Health Foundation RNA, vitamin K(Super K), Kidney Support RNA, nettle, boswellia, Behavior Support RNAs and skullcap may help to balance the body so that these mediators are less of an issue. In addition curcumin and green tea may be helpful for COMT V158M - - individuals.

In addition to its reported effect on IL6, vitamin K (Super K) may also be useful in supporting blood sugar imbalances. The + + marker for the VDR (vitamin D receptor) has been associated with potential blood sugar issues. Vitamin D levels are also closely tied to a variety of neurological conditions. Based on recent literature individuals should consider supplementing with at least 1000 IU of supplemental vitamin D daily. Also the use of ¼ dropper of ProLongevity RNA has proven to be helpful for many individuals. Vitamin K (Super K) and supplements to support the pancreas should also be considered such as OraPancreas, Gymnema sylvestre and Super Digestive enzymes. It would also be wise to monitor levels of chromium on an essential mineral test and consider supplementation if levels are low. In addition, to effects on blood sugar, variations in the VDR Fok marker reflect differences in bone mineral density. While increased bone mineral density is associated with increased calcium absorption it has also been associated with higher blood concentrations of lead.

I initially suggested the use of CCK (Resist Fat Apex Lean) to aid in supporting the pancreas. For mere pancreatic support it should be sufficient to use 1/4 to 1/2 CCK, the CCK Support RNA (1/8 dropper), OraPancreas (2 per day), Super Digestive enzymes with meals, and gymnema sylvestre.

In addition to its role in pancreatic support, CCK also appears to aid in addressing chronic bacterial loads in the body. As a result, the dose that is tolerated will depend in part on the bacterial load in your system. In order to use the CCK to address chronic bacterial issues it may require a much higher dose than the 1/4 tablet used only for pancreatic support. I suggest that you consider increasing the dose slowly from the 1/4 per day. You will get a sense over time of the maximum dose needed to help to aid in chronic bacterial issues. I suggest you consider starting with the 1/4 tablet along with 1/8 dropper CCK Support and gradually increase the CCK (Resist Fat Apex Lean) tablet by 1/4 amounts over time.

Individuals showing elevated oxalic acid along with elevated triglycerides on lab work may indicate a need for both pancreatic as well as liver support. Liver support can include OraLiv, Milk Thistle and Dandelion Root.

In addition to effects on blood sugar levels, decreased pancreatic activity may be associated with increased levels of oxalic acid as measured on organic acid tests. Supplementation to support healthy blood sugar levels and the pancreas may also be helpful in normalizing increased oxalic acid. In addition the use of the herbs Sheep sorrel and Turkey rhubarb may contribute to elevated levels of oxalic acid.

On a related note, pantothenic acid, molybdenum and quercetin (not for COMT V158M + +) may be helpful for elevated uric acid along with supplementation to support the kidneys (Kidney Support RNA, OraKidney, dandelion leaf).

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

- **Beginning the marathon**

Remember that as you begin to incorporate these suggestions into your program you should also monitor urines so that we can have a better understanding of any down slides as it may relate to detoxification as it is difficult to tell the difference between a negative reaction to a supplement and the behavioral impact of detoxification.

I would suggest that you wait to add Metals RNA until you have addressed any bacterial issues, supplemented the methylation cycle, and supported the mitochondria and the Kreb's cycle. I would continue to monitor urines on a regular basis as I expect that implementation of these suggestions will lead to detoxification of metals. Over time if this level of detoxification is not sufficient, you may want to progress to more active detoxification with the use of Metals RNAs (metals 1 through 5) as well as some of the other viral support for more enhanced metal excretion that is discussed in the autism book, the DVDs and the Supplement video. Alternatively if the supplementation suggested in this document is sufficient as based on behaviors as well as metal excretion judged by the graphing of urine toxic metal data, then I would suggest progressing at that time to Step 3 of the program, which is again described in the autism book, the DVDs and the Supplement video.

Remember, this is a program and a process not simply a laundry list of supplements for you to take. It does require that you take the time to read, then reread, understand and embrace the content of this document. Knowledge is power; the more information you have the better positioned you will be to use the tools you now have.

Read it, learn it, live it…

Sincerely,

Dr. Amy Yasko, Neurological Research Institute

The analysis from these tests is not comprehensive, as these results do not rule out additional mutations in enzymes that have been characterized but may not have been included in these tests.

Please note: Supplements are not meant to treat or cure disease. In addition, supplementation suggestions are not meant to diagnose, treat or cure disease. This information is presented by an independent medical expert whose sources of information include studies from the world's medical and scientific literature, client records, and other clinical and anecdotal reports. All dosages suggested are based on the author's personal experiences. It is important to note that each person's body type and tolerance levels to supplements may be somewhat different. The publisher, author, and/or experts specifically cited in this publication are not responsible for any consequences, direct or indirect, resulting from any reader's action(s). This document is not intended to be a substitute for consultation with a health care provider. You, the reader are instructed to consult with your personal health care provider prior to acting on any suggestions contained in this document. The purpose of this document is to educate the reader. The material in this document is for informational purposes only and is not intended for the diagnosis or treatment of disease.

Content and diagrams may not be reproduced without express permission from NRI and HHI