THE POWER OF METHYLATION

Critical consideration for optimizing care.

Bridget Briggs, MD ABIHM
Legal Disclaimer

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Learning Objectives

• Explain the impact of methylation on clinical outcomes.
• Illustrate the significance of the 10 SNPs chosen for the CORE panel.
• How clinical patterns are affected by the SNP.
Is Genomics the Key?

- Limitations that we face today in traditional Western medicine
- Add a new dimension of understanding to medicine
- What problems do we face implementing Genomics?
- Review safe and effective strategies to implement Clinical Genomics
Limitations We Face in Traditional Western Based Medicine

- Protocol-driven rather than personalized, precise, or solution-based.
- Standard of care dictates medications are used to treat acute and chronic diseases with minimal efforts on prevention and genomic individuality.
- Limited understanding of nutrigenomics, lifestyle medicine, toxigenomics, and epigenetic influences on disease states and progression.
- Patient frustrations.
The Application of Clinical Genomics and Metabolomics to Access Balance
Nutrigenomic Approach to Treatment

- Supplements
- Lifestyle
- Assessments, Genetic & Lab Tests
Express your Best DNA

Genes Turn **On & Off** Based On Your Environment!
Consider Methylation Genomics…

• Why is methylation balance so important?
• Why does methylation balance affect so many health conditions?
• Effective tools utilized in treating methylation imbalances.
What Is Methylation?

Important component in numerous cellular processes:

- Embryonic Development
- Detoxification
- Regulation of Enzyme Production
- Genomic Imprinting
- Preservation & Repair of Chromosome Stability

Methylation occurs a billion times per second in your body, it is important to optimize!
Can Adding Methyl Donors Change Cellular Replication?

In these cells, the Green Fluorescent Protein production is a readout of gene activity. By adding Methyl Groups gene activity was diminished and the green emitted light was reduced.
As you turn the control knob, egigenetic tags come and go to change the shape of the gene. Notice what happens to the mRNA and protein levels when you manipulate the epigenetic tags on the genes. Gene, mRNA, and protein production are linked. They change together.
Can the Removal of Methyl Groups Change Cellular Replication?

In these cells, GFP production is a readout of gene activity.
Gene Control

The addition of a de-methylator increased the express of the Green Fluorescent Protein and the emission of the green light was enhanced.
Gene Control & Cancer

Normal: regulated cell growth

Cancer: uncontrolled cell growth

Less methyl - genes ON

More methyl - genes OFF
Methylation and Imprinting
Licked Rat Pups vs. Non-Licked Pups

Nurturing Mom
• Licking, grooming, nursing
• Calm adults

Non-Nurturing Mom
• Ignored pups
• Anxious adults
Gene Expression

Deep in the brain of a newborn rat pup, methyl molecules silence the Glucocorticoid Receptor Gene. When it’s active, the GR gene produces a protein that helps the body relax after a stressful event. The type of care a pup receives from its mother during the first week of life can change the expression of this gene longterm. The more a mother licks her pups the more the methyl tags are removed and the GR protein is expressed calming the pups.
Gene Expression

Licking and grooming a pup removes methyl tags and the GR gene becomes more active. This will make it a little bit easier for the pup to relax after stress. The pup’s GR gene will most likely look like this for the rest of its life. In fact, the amount of nurturing the pup receives will have a major impact on its adult personality.
Glucocorticoid Receptor (GR) Helps Shut Down the Stress Response
Methyl-Sensitive Individuals Can Be Associated with High Anxiety

COMT Val 158 Met
Impaired Methylation transfer via catechol-O-methyltransferase enzyme

• May lead to excess Methyl tags
• Has been associated with Hyper Alert state
• Excess Fight or Flight Response
• Patients report lifelong hypersensitivity to Stress and Life Changes
• Wired and Tired
• Worrier and Warrior
Epigenetic Patterns are Reversible

Inject a drug that adds methyl tags

Relaxed, high-nurtured rat

Anxious rat
Methyl-Sensitive Individuals

Caution is recommended in Methyl Sensitive Individuals
Avoid excessive dosing of Methyl Groups
Methyl-Cobalamine
Methyl-Folate
Tri-methyl-glycine
Betaine
Magnesium glycinate
Turmeric
Caffeine
Methyl-phenidate
Calming Methyl-Sensitive Individuals

- Valproic Acid has been used in seizure disorder as well as mood disorders including depression and Anxiety.
- Niacin is a well known De-Methylator which can be used to rescue a patient from an overstimulation event after taking too many methyl groups.
- Phosphatidylserine can be a huge support to such individuals. (Vayarin studied in children with ADHD and impulsivity)
A Different Kind of Inheritance

A pup that is raised by an anxious, low-nurturing mother becomes an anxious adult.

A pup that is raised by a relaxed, high-nurturing mother becomes a relaxed adult.
Lick the Rat

Antepartum Bonding
• Affects Methylation patterns of the GR gene.
• Affects long term personality type.

Methylation Patterns
• Affected by appropriate methyl donors, stress & bonding.
• Early epigenetic patterns can have long lasting effects.
Prenatal Methylation of the Epigenome

Pregnant Agouti mouse supplemented with methylfolate enriched water.

All progeny have the suppression of the Agouti gene such that all mice are normal skin color, no diabetes or obesity.
Eating for Two

- Agouti Gene
  - Obese
  - Prone to cancer and diabetes

- Agouti Gene with methyl groups
  - Thin
  - Healthy

(eatingfor2挪威.com)
Of Toxins and Supplements

These two mice are genetically identical and same age. While pregnant, they were fed BPA, but DIFFERENT DIETS.

- Normal Mouse Diet
- Diet supplement with choline, folic acid, betaine & B12

Photo by Randy L. Jirtle PhD
Women with PCOS

- Serum levels of BPA are 8 fold higher than the general population
- BPA and other Dioxins are known hormone disrupters
- Primary pathway of detoxification is via Phenol SulfoTransferase Enzymes (SULT enzymes)
- Toxic intermediates of BPA-S have a high affinity for the thyroid gland and are known thyroid disruptors
Grandparents Count

Food abundance for the grandfather was associated with a reduced lifespan for the grandchildren as compared to food shortage was associated with longer lifespan in their grandchildren.
A Bee’s Royal Diet

Larva fed Royal Bee Jelly receive Methyl groups that silence specific Genes associated with Drones and lead to the development of the Queen Bee.
The Challenges of Proving Epigenetic Inheritance
Medical Interventions Altering Methylation

Seizure medications are known demethylators.

Fenofibrate medications are known demethylators.

Niacin causes demethylation.

cancer therapies affect methylation.

immunomodulators such as Methotrexate affect
Environmental Influences on Methylation...
Alcohol Metabolism and Epigenetics Changes

Alcohol, including those generated during ethanol metabolism, can impact disease states by binding to transcription factors and/or modifying chromatin structure, thereby altering gene expression patterns. For example, the activities of enzymes involved in epigenetic modifications such as DNA and histone methylation and histone acetylation, are influenced by the levels of metabolites such as nicotinamide adenine dinucleotide (NAD), adenosine triphosphate (ATP), and S-adenosylmethionine (SAM). Chronic alcohol consumption leads to significant reductions in SAM levels, thereby contributing to DNA hypomethylation. Similarly, ethanol metabolism alters the ratio of NAD+/NADH and promotes the formation of reactive oxygen species (ROS) and acetaldehyde, all of which impact epigenetic regulatory mechanisms. In addition to altered carbohydrate metabolism, induction of cell death, and changes in mitochondrial permeability transition, these metabolite-related changes can lead to modulation of epigenetic regulation of gene expression. Understanding the nature of these epigenetic changes will help researchers design novel medications to treat or at least ameliorate alcohol-induced organ damage. Key words: Alcohol consumption; alcohol metabolism; ethanol metabolism; alcohol-induced organ damage; disease; epigenetics; epigenetic mechanisms; epigenetic modifications; gene expression; DNA, RNA methylation; histone modification; histone acetylation.
The Role of Epigenetics in the Latent Effects of Early Life Exposure to Obesogenic Endocrine Disrupting Chemicals.

Stel J¹, Legler J¹.

Abstract
Recent research supports a role for exposure to endocrine-disrupting chemicals (EDCs) in the global obesity epidemic. Obesogenic EDCs have the potential to inappropriately stimulate adipogenesis and fat storage, influence metabolism and energy balance and increase susceptibility to obesity. Developmental exposure to obesogenic EDCs is proposed to interfere with epigenetic programming of gene regulation, partly by activation of nuclear receptors, thereby influencing the risk of obesity later in life. The goal of this minireview is to briefly describe the epigenetic mechanisms underlying developmental plasticity and to evaluate the evidence of a mechanistic link between altered epigenetic gene regulation by early life EDC exposure and latent onset of obesity. We summarize the results of recent in vitro, in vivo, and transgenerational studies, which clearly show that the obesogenic effects of EDCs such as tributyltin, brominated diphenyl ether 47, and polycyclic aromatic hydrocarbons are mediated by the activation and associated altered methylation of peroxisome proliferator-activated receptor-γ, the master regulator of adipogenesis, or its target genes. Importantly, studies are emerging that assess the effects of EDCs on the interplay between DNA methylation and histone modifications in altered chromatin structure. These types of studies coupled with genome-wide rather than gene-specific analyses are needed to improve mechanistic understanding of epigenetic changes by EDC exposure. Current advances in the field of epigenomics have led to the first potential epigenetic markers for obesity that can be detected at birth, providing an important basis to determine the effects of developmental exposure to obesogenic EDCs in humans.
Conditions Affected by Methylation

Research has linked errors in methylation to a variety of consequences, including several human diseases such as:

- Cancer
- Diabetes
- Heart Disease
- Autoimmune
- Chronic Conditions
- Alzheimer’s
Methylation Cycle Review

- Energy Balance
- Blood Sugar Balance
- Allergy / Immune Balance
- Sleep Cycles
- Antioxidant Status
- Mitochondrial Function
- Nitric Oxide Cycle
- Gut Barrier Health Status
- Thyroid, Adrenal, & Sex Hormone Cycles
- Detoxification
- Sympathetic/Parasympathetic
Beyond MTHFR ....

- **HETEROZYGOUS**
  - MTHFR C677T
  - 40% loss of function

- **HOMOZYGOUS**
  - MTHFR C677T
  - 70% loss of function

- **COMPOUND HETEROZYGOUS**
  - MTHFR C677T & MTHFR A1298C
  - 50% loss of function
Enzyme Function of Core SNPs Affecting Methylation Status

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Function and Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTHFR</td>
<td>Produces 5-methyltetrahydrofolate (5-MTHF).</td>
</tr>
<tr>
<td>MTR</td>
<td>Recycles homocysteine back into methionine. This enzyme is B12 dependent.</td>
</tr>
<tr>
<td>MTRR</td>
<td>Recharges MTR via re-methylation. This enzyme is B12 dependent.</td>
</tr>
<tr>
<td>BHMT</td>
<td>Catalyzes the conversion of betaine and homocysteine to dimethylglycine and methionine. This is one of two biochemical pathways involved in recycling homocysteine.</td>
</tr>
<tr>
<td>CBS</td>
<td>Catalyzes the conversion of homocysteine to cystathionine, the first step in the transsulfuration pathway which ultimately involves the degradation of sulfur-containing amino acids. B6 is a cofactor.</td>
</tr>
<tr>
<td>Enzyme</td>
<td>Function</td>
</tr>
<tr>
<td>--------</td>
<td>----------</td>
</tr>
<tr>
<td>VDR</td>
<td>Vitamin D receptor is involved in mineral metabolism, immune function and dopamine synthesis.</td>
</tr>
<tr>
<td>COMT</td>
<td>Catalyzes phase II detoxification (metabolism) of neurotransmitters dopamine, epinephrine, and norepinephrine, as well as estrogen.</td>
</tr>
<tr>
<td>MAO-A</td>
<td>Catalyzes the oxidative deamination (inactivation) of amines, such as tyramine, dopamine, norepinephrine and serotonin.</td>
</tr>
<tr>
<td>MAO-B</td>
<td>Catalyzes the oxidative deamination (inactivation) of biogenic and xenobiotic amines, specifically epinephrine and histamine, as well as dopamine.</td>
</tr>
<tr>
<td>NOS</td>
<td>Encodes for nitric oxide synthases which catalyze the reaction of oxygen with L-arginine generating citrulline and nitric oxide.</td>
</tr>
</tbody>
</table>
Interplay of Gears

Krebs
Nitric Oxide
Biopterin
Folate
Methionine
Transsulfuration
Where is the wrench impacting your patients’ health?
Diagnostics & Assessments

- Base Line
  - Chemistry
  - Metabolic
  - Endocrine
- Micro Nutrients
- Food Allergies
- Neurotransmitters
- Cardiac Risk
- Genetic SNPs:
  - MTHFR
  - COMT
  - CBS
  - MTR
  - MTRR
  - BHMT
  - MAO (A & B)
  - VDR
  - NOS
## Genotyping

<table>
<thead>
<tr>
<th>Panel</th>
<th>Gene</th>
<th>Position (NCBI dbSNP*)</th>
<th>Ancestral Allele</th>
<th>Result</th>
<th>Special Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylation</td>
<td>COMT</td>
<td>p.Val158Met rs4680</td>
<td>G</td>
<td>AG</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>MTHFR</td>
<td>A1298C rs1801131</td>
<td>A</td>
<td>AA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MTHFR</td>
<td>C677T rs1801133</td>
<td>C</td>
<td>TT</td>
<td>++</td>
</tr>
<tr>
<td>Vitamin D3</td>
<td>VDR</td>
<td>c.1024+283G&gt;A rs1544410</td>
<td>G</td>
<td>GG</td>
<td></td>
</tr>
<tr>
<td>Homocysteine Metabolism</td>
<td>VDR</td>
<td>c.1056T&gt;C rs731236</td>
<td>T</td>
<td>TT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CBS</td>
<td>c.699C&gt;T rs234706</td>
<td>G</td>
<td>AG</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MTR</td>
<td>c.2756A&gt;G rs1805087</td>
<td>A</td>
<td>AG</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MTRR</td>
<td>c.666A&gt;G rs1801394</td>
<td>A</td>
<td>AA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BHMT</td>
<td>p.Arg239Gln rs37733890</td>
<td>G</td>
<td>GG</td>
<td></td>
</tr>
<tr>
<td>Nitric Oxide Synthesis</td>
<td>NOS3</td>
<td>c.894T&gt;G rs1799983</td>
<td>G</td>
<td>GG</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NOS3</td>
<td>g.6933C&gt;T rs2070744</td>
<td>C</td>
<td>CT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NOS2</td>
<td>p.Ser608Lue rs2297518</td>
<td>G</td>
<td>GG</td>
<td></td>
</tr>
<tr>
<td>Catecholamine Metabolism</td>
<td>MAOA</td>
<td>p.Arg297= rs6323</td>
<td>T</td>
<td>GG</td>
<td>+--</td>
</tr>
<tr>
<td></td>
<td>MAOB</td>
<td>g.118723A&gt;G rs1799836</td>
<td>A</td>
<td>AA</td>
<td>++</td>
</tr>
</tbody>
</table>

*The ancestral allele is assigned based on genome database information provided by Ensembl (www.ensembl.org) and refers to the DNA sequence first present in the gene pool.

Follow the below instructions for reference articles on specific SNPs:
2. Type in the ref in this format: "rs###" and click Search.
3. On the webpage for the each SNP, click on the "PubMed" link to access publications related to that SNP.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Low</th>
<th>Normal</th>
<th>Elevated</th>
<th>High</th>
<th>Commonly Associated Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Anxiousness, Low mood, Intestinal complaints, Low libido, Discomfort, Sleep difficulties, Weight issues, Menopause symptoms, Vasomotor reactions</td>
</tr>
<tr>
<td>GABA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Excess energy, Anxiousness, Sleep difficulties, Norepinephrine depletion in the brain</td>
</tr>
<tr>
<td>Glutamate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low glutamate may be an indicator of low immune activation. Focus issues may be possible.</td>
</tr>
<tr>
<td>PEA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Focus issues, Fatigue, Memory issues, Weight issues</td>
</tr>
<tr>
<td>Dopamine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Anxiousness, Focus issues, Sleep difficulties, Weight issues, Vascular issues, Immune stress</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Focus issues, Fatigue, Low libido, Weight issues</td>
</tr>
</tbody>
</table>

Notes:
<table>
<thead>
<tr>
<th>TESTS</th>
<th>RESULT</th>
<th>FLAG</th>
<th>UNITS</th>
<th>REFERENCE INTERVAL</th>
<th>LAB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neopterin, Urine</td>
<td>20</td>
<td>Low</td>
<td>ng/mg creat</td>
<td>134 - 492</td>
<td>01</td>
</tr>
</tbody>
</table>

For investigational use only.
<table>
<thead>
<tr>
<th>Compound Tested</th>
<th>Results (mcg/mg creatinine)</th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
<th>4th</th>
<th>5th</th>
<th>95% Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neopterin</td>
<td>0.31</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.15-0.79</td>
</tr>
<tr>
<td>Biopterin</td>
<td>0.56 (H)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.04-0.35</td>
</tr>
</tbody>
</table>
0088 Neopterin/Bioppterin Profile - Urine

Methodology: LC/Tandem Mass Spectroscopy, Colorimetric

<table>
<thead>
<tr>
<th>Compound Tested</th>
<th>Results</th>
<th>Quintile Ranking</th>
<th>95% Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neopterin</td>
<td>0.39</td>
<td>0.18</td>
<td>0.15-0.79</td>
</tr>
<tr>
<td>Biopterin</td>
<td>&lt;DL</td>
<td>0.05</td>
<td>0.04-0.35</td>
</tr>
<tr>
<td>Ratio</td>
<td>2.03</td>
<td>0.76</td>
<td>0.04-8.67</td>
</tr>
</tbody>
</table>

Note: the “<DL” sign indicates an approximate value due to the “<DL” result.
# Methylation Profile: plasma

<table>
<thead>
<tr>
<th>PRIMARY &amp; INTERMEDIATE METABOLITES</th>
<th>RESULT/UNIT</th>
<th>REFERENCE INTERVAL</th>
<th>PERCENTILE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methionine</td>
<td>1.7 μmol/dL</td>
<td>1.6–3.6</td>
<td></td>
</tr>
<tr>
<td>Cysteine</td>
<td>23 μmol/dL</td>
<td>20–38</td>
<td></td>
</tr>
<tr>
<td>S-adenosylmethionine (SAM)</td>
<td>66 nmol/L</td>
<td>86–145</td>
<td></td>
</tr>
<tr>
<td>S-adenosylhomocysteine (SAH)</td>
<td>24.0 nmol/L</td>
<td>10–22</td>
<td></td>
</tr>
<tr>
<td>Homocysteine</td>
<td>7.0 μmol/L</td>
<td>&lt;11</td>
<td></td>
</tr>
<tr>
<td>Cystathionine</td>
<td>0.01 μmol/dL</td>
<td>&lt;0.05</td>
<td></td>
</tr>
</tbody>
</table>

## METHYLATION INDEX

<table>
<thead>
<tr>
<th>RESULT</th>
<th>REFERENCE INTERVAL</th>
<th>PERCENTILE</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAM : SAH</td>
<td>&gt; 4</td>
<td></td>
</tr>
</tbody>
</table>

CLINICAL INTERPRETATION:

**Methionine**: Low

**Cysteine**: Low

**S-adenosylmethionine (SAM)**: Low

**S-adenosylhomocysteine (SAH)**: Low

**Homocysteine**: Low

**Cystathionine**: Low

**SAM : SAH**: Low
<table>
<thead>
<tr>
<th>Component</th>
<th>Result</th>
<th>Units</th>
<th>Flag</th>
<th>Range</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neopterin, Urine</td>
<td>25</td>
<td>ng/mg creat</td>
<td>L</td>
<td>134-492</td>
<td>For investigational use only</td>
</tr>
</tbody>
</table>

**Send to PSC (Collection Date: 09/24/2016 10:00, Status: Final)**

Performed At: SO, LabCorp San Diego
13112 Evening Creek Dr So Ste 200, San Diego, CA, 921284108
Jenny, Galloway, MD, Phone: 8586683700
### Patient Details
- **DOB:** 03/30/1944
- **Gender:** M
- **SSN:** 479873
- **Patient ID:** PRO912434

### Clinical Info
- **CC:** 9513022552
- **Total Volume:** Not Provided

### Alternate Control Number
- **Neopterin, Urine**

### Specimen Details
- **Date collected:** 01/23/2017
- **Date entered:** 01/23/2017
- **Date reported:** 01/26/2017

### Results Table

<table>
<thead>
<tr>
<th>TESTS</th>
<th>RESULT</th>
<th>FLAG</th>
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<td></td>
</tr>
</tbody>
</table>

### Additional Information
For investigational use only.

### Physician Details
- **Ordering:** BRIGGS
- **Referring:**
- **ID:** 1568436343
- **NP:** 1568436343

### General Comments & Additional Information
A courtesy copy of this report has been sent to 9513022552.

### Ordered Items
- Neopterin, Urine
<table>
<thead>
<tr>
<th>Parameter</th>
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<tr>
<td>5-HIAA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GABA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taurine</td>
<td></td>
<td></td>
<td></td>
<td>Anxiousness, Sleep difficulties, Sympathetic fatigue, Cardiovascular stress</td>
</tr>
<tr>
<td>Glycine</td>
<td></td>
<td></td>
<td></td>
<td>Excess energy, Anxiousness, Sleep difficulties, Immune stress</td>
</tr>
<tr>
<td>Glutamate</td>
<td></td>
<td></td>
<td></td>
<td>Low glutamate may be an indicator of low immune activation. Focus issues may be possible.</td>
</tr>
<tr>
<td>Histamine</td>
<td></td>
<td></td>
<td></td>
<td>Intestinal complaints, Discomfort, Sleep difficulties</td>
</tr>
<tr>
<td>PEA</td>
<td></td>
<td></td>
<td></td>
<td>Focus issues, Fatigue, Memory issues, Weight issues</td>
</tr>
<tr>
<td>Dopamine</td>
<td></td>
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<td></td>
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Notes:
Unlike folate which is found naturally in food, folic acid (pteroylmonoglutamic acid) is the synthetic form of the vitamin used commercially in fortified foods and supplements. Excess folic acid supplementation can lead to a build-up of folic acid in serum, termed unmetabolized folic acid (UMFA). Folic acid supplementation has been associated with cancer progression and this may be due to high UMFA. Monitoring of UMFA has been recommended by researchers from the National Institutes of Health, Office of Dietary Supplements.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Low</th>
<th>Normal</th>
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<th>Commonly Associated Symptoms</th>
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Legend
Common Symptoms

- Headaches
- Cardiac Disease
- Cartilage/Collagen Anomalies
- Growth Anomalies
- Depression

MTHFR
Common Symptoms

MTR/MTRR

- Fatigue / Anemia
- Cardiac Disease
- Neuro Degeneration Association
- Neuro Tube Defects
- Depression
Common Symptoms

COMT

- Poor Stress Management
- Breast / Prostate Cancer
- Anxious
- Wired / Tired
- Cardio Disease
- Poor Detoxifier
- Chronic Fatigue
- Fibro
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Common Symptoms

CBS

GERD
SIBO
Myalgia / Tendinopathies
Poor Detoxifier
Cardiovascular Disease
Common Symptoms

NOS

- Hypertension
- Migraine
- Poor Wound Healing
- Cardiovascular Disease
- Reynaud's
Common Symptoms

MAO-A

- SSRI Non-Responder
- PMS
- Headaches
- Anxiety
- Depression
Common Symptoms

MAO-B

- OCD
- Allergies
- ADHD
- "Amine" Sensitive
- SSRI / "Amped"
Common Symptoms

VDR

Depression

Inflammed

Osteoporosis

Cardiovascular Disease

Fatigue
All patients have unique polymorphisms which alters the functioning of the gears.

Understanding genetic markers and pathways can lead to a new kind of medicine that is Precise, Personalized & Preventative!
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