



LAB #: B000000-0000-0  
 PATIENT: Sample Patient  
 ID: PATIENT-S-00000  
 SEX: Male  
 AGE: 45

CLIENT #: 12345  
 DOCTOR:  
 Doctor's Data, Inc.  
 3755 Illinois Ave  
 St. Charles, IL 60174 U.S.A.

## DNA Methylation Pathway Profile; Blood Spot

### RESULTS

Gene Name / Variation	Mutation Not Present	Mutation(s) Present	Call	
SHMT / C1420T		+/-	Hetero	Minus "-" represents no mutation
AHCY / 1	-/-		A	Plus "+" represents a mutation
AHCY / 2	-/-		T	"-/-" indicates there is no mutation
AHCY / 19	-/-		A	
MTHFR / C677T	-/-		C	"+/-" indicates there is one mutation
MTHFR / A1298C	-/-		A	"+/+" indicates there is a double mutation
MTHFR / 3	-/-		C	
MTR / A2756G		+/-	Hetero	
MTRR / A66G		+/-	Hetero	
MTRR / H595Y	-/-		C	
MTRR / K350A	-/-		A	
MTRR / R415T	-/-		C	
MTRR / S257T	-/-		T	
MTRR / 11		+/-	Hetero	
BHMT / 1	-/-		A	
BHMT / 2		+/-	Hetero	
BHMT / 4		+/+	C	
BHMT / 8		+/+	T	
CBS / C699T	-/-		C	
CBS / A360A	-/-		C	
CBS / N212N	-/-		C	
COMT / V158M		+/+	A	
COMT / H62H		+/+	T	
COMT / 61	-/-		G	
SUOX / S370S	-/-		CG	
VDR / Taq1	-/-		C	
VDR / Fok1	-/-		C	
MAO A / R297R	-/-		G	
NOS / D298E	-/-		G	
ACAT / 1-02		+/-	Hetero	

#### Comments:

Date Collected: 11/08/2012

Date Received: 11/13/2012

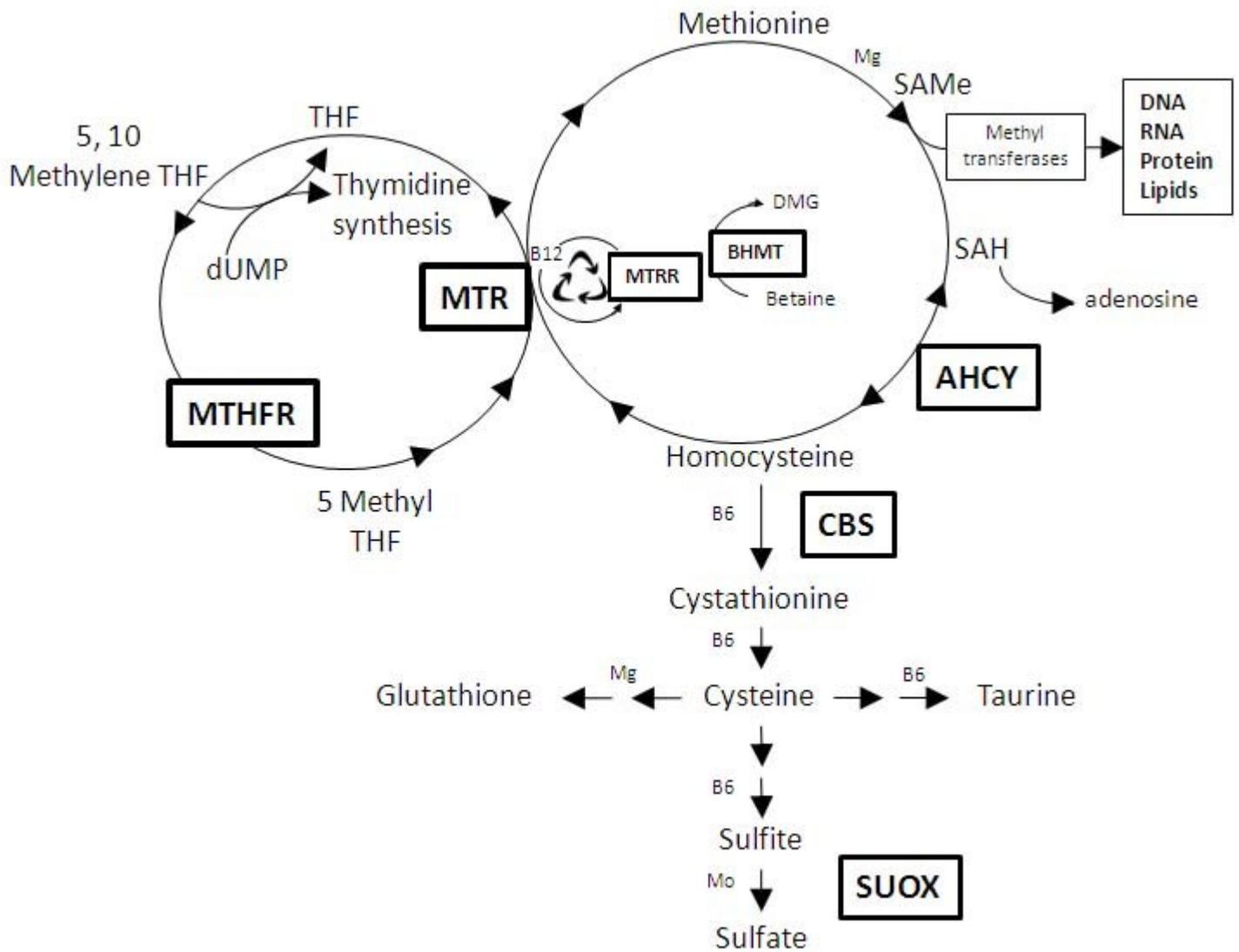
Date Completed: 12/10/2012

\*For Research Use Only. Not for use in diagnostic procedures.

Methodology: **MassARRAY iPLEX platform by Sequenom**

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## Methionine Metabolism Transmethylation & Transsulfuration Diagram



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## Introduction

Single nucleotide polymorphisms (SNPs) are DNA sequence variations, which may occur frequently in the population (at least one percent of the population.) They are different from disease mutations, which are very rare. Huntington's disease is an example of a disease mutation- if you inherit the altered gene, the disease will develop. Certain SNPs may be associated with particular health conditions, but they are not known to cause disease. The majority of SNPs in this report affect protein, enzyme or cell receptor structure or function. Some SNPs may have modest and subtle but true biological effects and have been correlated with health concerns or disease risk. Their abundance in the human genome as well as their higher frequencies in the human population have made them targets to help explain variation in risk of common diseases. Often multiple SNPs need to be present to alter metabolic or biochemical functions in the body. SNPs and gene expression may often be modified by epigenetic factors (diet, lifestyle, nutrition, toxicant exposures). The influence of a single SNP may vary widely: for example, a specific SNP in MTHFR may influence enzyme function from 30-60%. In contrast, the SNP with the greatest known effect on human height only accounts for 0.04 percent of height variations.

Individuals are classified as homozygous (+/+) for the variant if they carry 2 mutated alleles, heterozygous (+/-) if they carry only one mutated allele, and homozygous (-/-) for the wild type gene if they have no mutant alleles. This panel of SNPs provides information about many facets of health and wellness, with an emphasis on important biochemical processes such as methionine metabolism (see diagram on the preceding page), detoxification, hormone and neurotransmitter balance, and Vitamin D function.

It is emphasized that SNPs are not imminently associated with abnormal metabolism or disease conditions. The presence or absence of a reported SNP is not the sole determinant of physiological function; it is simply one potential contributing factor. The results presented in this report should be interpreted in context with symptoms, epigenetic factors and other laboratory findings.

## SHMT/ C1420T (Serine hydroxymethyltransferase)

### Pathways/biochemistry

Serine hydroxymethyltransferase (SHMT) catalyzes the inter-conversion of serine and glycine, which has a role in neurotransmitter synthesis and metabolism and, moderates the activity of S-adenosyl methionine (SAM) synthesis. SHMT converts tetrahydrofolate into 5,10-methylene tetrahydrofolate. Folate-dependent one-carbon metabolism is critical for the synthesis of numerous cellular constituents required for cell growth, and SHMT is central to this process. Vitamin B-6 is an obligatory cofactor for SHMT activity.

### Possible Health Implications

SHMT polymorphisms may disrupt cellular function leading to increased DNA damage, alterations in folate distribution for methylation reactions (inhibition of methylation), and competition with MTHFR. When

combined with MTHFR SNPs, SHMT SNPs may be associated with elevated plasma homocysteine which increases risk for cardiovascular disease, stroke, vascular dementia, and Alzheimer's disease; these cumulative effects are dependent on B-vitamin and folate status.

The maternal risk for Down's Syndrome is also altered with the SHMT mutation; the CC genotype is protective.

SHMT C1420 T genotypes may generally be considered protective for cancers, however the homozygous (TT) genotype may increase risk for colorectal cancers in cases of folate deficiency. The cancer protective effects of CT/TT genotypes may prove to be folate-dependent; research is ongoing. There is evidence that both SHMT/ C1420T and MTRR/ A66G polymorphisms may decrease risk for autism.

In general, homozygotes are more influenced by SNPs than heterozygotes.

How to optimize the phenotype

Ensure adequate B-12, folate, betaine and B-6 to support methylation pathways. Monitor homocysteine levels and methylation pathways. Minimize cancer risks through lifestyle interventions.

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MTR/A2756G (methionine synthase)

Pathways/biochemistry

Methionine synthase (MTR) catalyzes the re-methylation of homocysteine to methionine utilizing methylcobalamin (methyl B-12) as a cofactor. Important in folate metabolism, MTR maintains intracellular levels of methionine which is the precursor to S-adenosylmethionine (SAM). SAM is a vital methyl group donor involved in hundreds of methylation reactions, including methylation of DNA. Studies indicate that methionine synthase reductase (MTRR) may be required as a molecular chaperone for proper MTR function.

#### Possible Health Implications

Under- or over-methylation of the DNA for tumor suppressor or promoter genes may contribute to the selective growth or transformation of cells. Approximately 50% of cancer cell types are methionine dependent; low MTR function, while increasing plasma homocysteine levels, would decrease available methionine; this may influence cancer risk and tumor growth.

The MTR/A2756G polymorphism has been associated with increased maternal risk of neural tube defect; the risk increases with the number of high-risk alleles, and may be cumulative with MTHFR polymorphisms. The risk of hyperhomocysteinuria is also increased. A plasma homocysteine level greater than 14  $\mu\text{mol/L}$  is associated with increased risk of Alzheimer's disease.

MTR/A2576G is associated with male infertility and, it is more prevalent in patients with Celiac Disease. The SNP is generally cancer-protective (GI tract, lymphomas), and may be protective against dementia in the AG or GG genotypes; this protection may be population-specific to those of European descent and the reverse may be true of Asian populations. The AG/GG phenotype is associated with folate-deficient hypertension in Chinese males and, with increased risk of Inflammatory Bowel Disease in Asians.

#### Genotypic/Phenotypic expression

There is mounting evidence that, especially within the folate and methylation pathways, multiple SNPs in multiple genes (haplotypes) and/or low folate or B-vitamin status are necessary to alter metabolism or change health outcomes. MTR may have cumulative effects with MTHFR/C677T, MTRR/A66G, AHCY or CBS polymorphisms.

In general, homozygotes are more influenced by SNPs than heterozygotes.

#### How to optimize the phenotype

Provide adequate B-12 (or methylcobalamin) and nutritional support for methylation pathways. Minimize cancer risks with lifestyle interventions.

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#### MTRR A66G/H595Y/K350A/R415T/S257T/11 (methionine synthase reductase)

#### Pathways/biochemistry

Methionine synthase reductase (MTRR) is one of two enzymes involved in the regeneration of methionine (with MTR) from homocysteine. MTRR regenerates methionine synthase (MTR) via a methylation reaction that uses S-adenosylmethionine (SAM) as a donor. MTRR further supports methionine synthase (MTR) activity by "recycling" vitamin B-12. Studies indicate that MTRR may also be required as a molecular chaperone for proper methionine synthase (MTR) function.

#### Possible Health Implications

MTRR/A66G produces an MTRR enzyme with a lower affinity for MTR and some studies have found it to be associated with homocysteine levels; further studies have shown that MTR requires MTRR to function properly. The 66AG/GG SNPs are also associated with increased micronucleation, a marker for chromosome damage and developmental delays.

MTRR/66 AA is considered a risk factor for folate-related neural tube defects and increased risk of Down's

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syndrome, specifically as a maternal risk factor when homocysteine levels are high. MTRR/66 AA is associated with a higher rate of micronucleation, a marker for cell damage and developmental delays. The rate of micronucleation increases with a history of smoking. MTRR/66 AA is more frequently associated with symptoms of Autism Spectrum Disorder(ASD).

MTRR/66GG is associated with male infertility (as are MTHFR and MTR). Polymorphisms in MTRR- /66/AG/GG and /H595Y-have been associated with the risk of cancers (breast, colon, prostate, pancreatic); the 66GG SNP appears to reduce the risk of acute lymphoblastic leukemia and, Alzheimer disease.

MTRR/66 AG/GG is associated with an increased risk of gastric cancers -this association is currently only documented for Asian populations (Korean); the risk increases further with obesity. MTRR/A66G polymorphism may reduce risk for autism.

There is mounting evidence that, especially within the folate and methylation pathways, multiple SNPs in multiple genes (haplotypes) and low folate or B-vitamin status are necessary to alter metabolism or change health outcomes. MTRR polymorphisms may have cumulative effects with MTHFR/C677T, MTR, AHCY or CBS polymorphisms.

The clinical significance of MTRR polymorphisms /K350A/, R415T, /S257T, and /11 is currently unknown; research is ongoing.

In general, homozygotes are more influenced by SNPs than heterozygotes.

How to optimize the phenotype

Provide adequate B-12, folate and nutritional support for methylation pathways. Hydroxycobalamin may be the preferred form of B-12 for this SNP. Minimize cancer risks with lifestyle interventions.

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### BHMT 1,2,3,4 (betaine-homocysteine methyltransferase)

#### Pathways/biochemistry

Betaine-homocysteine methyltransferase (BHMT) catalyzes the transfer of a methyl group from betaine to homocysteine to produce methionine and dimethylglycine. This is commonly referred to as the "short route" in the regeneration of methionine from homocysteine. The "long route" requires folate (MTHFR) and B-12 (MTR and MTRR). BHMT and its polymorphisms are involved in the regulation and metabolism of homocysteine. The BHMT pathway is folate-independent, although levels of folate, choline, and dimethylglycine (DMG) are predictive for plasma betaine levels. DMG inhibits BHMT by product inhibition, but does not affect the BHMT2 variant. The enzyme is found almost exclusively in liver and kidney tissues; the reaction is involved in choline oxidation as well as the methylation of homocysteine. The BHMT-2 polymorphism product is rapidly degraded unless it is bound to BHMT and is stabilized by homocysteine to become a functional product. BHMT2 cannot use betaine, rather it converts homocysteine to methionine using S-methylmethionine as a methyl donor. Methionine levels regulate BHMT2 activity by product inhibition.

#### Possible Health Implications

BHMT and its polymorphisms are involved in the regulation and metabolism of homocysteine. BHMT has been reported to protect the liver from homocysteine-induced injury. Elevated levels of homocysteine are a known risk factor for vascular disease and neural tube defects. Elevated circulating homocysteine levels are also being studied as a possible risk factor for osteoporosis, dementia, and complications of pregnancy. Animal studies have shown BHMT2 to be protective, with adequate nutrition, against acetaminophen-induced liver toxicity.

Preliminary research indicates that BHMT1 may have some function in immune response and reactivity.

#### Genotypic/Phenotypic expression

Polymorphisms will likely be present with altered elevated homocysteine levels.  
In general, homozygotes are more influenced by SNPs than heterozygotes.

#### How to optimize the phenotype

Consider the DDI Methylation Profile to assess the components of the methylation pathway. Zinc-dependent BHMT requires adequate levels of betaine to function optimally. Support the methionine synthase dependent methylation pathway ("Long route") with adequate B-12 and folate.

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We have never put a color diagram in commentaries. This is useful but perhaps we can re-do in black and white.

#### COMT V158M, H62H, 61 (catechol-O-methyltransferase)

##### Pathways/biochemistry

Catechol-O-methyltransferase catalyzes the transfer of a methyl group (using SAM as the methyl donor), an important step in the inactivation of biological and xenobiotic catechols.

COMT is found in nerve cells, and in the liver, kidneys and red blood cells. In the brain COMT functions to break down catecholamine neurotransmitters such as dopamine, epinephrine, and norepinephrine. In the liver, COMT helps inactivate 2- and 4-hydroxyestrogens prior to excretion in bile.

##### Possible Health Implications

SNPs in COMT/ V158M/ H62H may affect neurologic processes (particularly prefrontal processing), including mood and pain tolerance. The V158M VV homozygous variant is associated with deviations in thought processes that are common in people with schizophrenia, including problems with working memory, inhibition of behavior, and attention. The V158Met polymorphism has also been associated with other disorders that affect thought (cognition) and emotion. It is still being evaluated as a risk factor for bipolar disorder, panic disorder, anxiety, obsessive-compulsive disorder (OCD), eating disorders, and attention deficit hyperactivity disorder (ADHD).

COMT plays a key role in processes associated with the placebo effect such as reward, pain, memory and learning. The homozygous COMT /V158M (MM) has the strongest placebo response.

COMT function will affect the half-life of neurologic pharmaceuticals such as L-Dopa, alpha-methyl DOPA and isoproterenol, as well as some asthma medications and anti-hypertensives. Polymorphism of V158M in the COMT gene has been related to increased cancer risk. In the liver, COMT helps inactivate 2- and 4-hydroxyestrogens prior to excretion in bile. SNPs may affect the efficiency of COMT function; increased enzyme function may be protective against benign prostatic hypertrophy and other hormone-mediated diseases. The V158M variant (MM) confers low COMT activity and contributes to postmenopausal breast cancer in women, particularly those with a higher body mass index.

##### Genotypic/Phenotypic expression

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There is a decrease in enzyme function in COMT/V158M with methionine substitution, with up to a four-fold decrease in enzyme function for V158M homozygotes (MM).

In general, homozygotes are more influenced by SNPs than heterozygotes, and multiple COMT polymorphisms may increase the likelihood for adverse effects. COMT polymorphisms may have cumulative effects with MAO A polymorphisms.

How to optimize the phenotype

Adjust medication dosages to accommodate difference in enzyme functions. Minimize cancer risks through lifestyle interventions. Evaluate risks of hormone therapies with COMT/V158M genotypes prior to implementation.

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ACAT /1 (acetyl coenzyme A acetyltransferase)

Pathways/biochemistry

ACAT is an enzyme found both in the cytoplasm (ACAT/2) and the mitochondria (ACAT/1). ACAT/1 is found in all tissues except intestinal tissue; ACAT/2 is found primarily in intestinal tissues. The ACAT/1 enzyme (mitochondrial) plays an important role beta-oxidation of fatty acids and protein metabolism; it is a step in the metabolic pathway for the amino acid isoleucine, and contributes to cellular energy production. ACAT/1 also completes ketone metabolism, synthesizing acetyl-Co-A for energy production.

ACAT/2 encodes a similar enzyme in the cytosol which is involved in the early steps of cholesterol biosynthesis and lipid metabolism.

Possible Health Implications

Polymorphism in ACAT/1 may increase the level of organic acids in the blood. Ketoacidosis may result from increased organic acidemia and may damage body tissues and organs, such as the nervous system. Mutations in ACAT/1 may cause the condition beta-ketothiolase deficiency. ACAT/1 may also be involved in foam cell formation and atherosclerosis.

Genotypic/Phenotypic expression

Based solely on the mutation, ACAT/1 may function poorly or not at all. However, published research indicates that genotype alone does not predict expression of the disorder; most patients develop normally and are able to manage symptoms. In general, homozygotes are more influenced by SNPs than heterozygotes.

How to optimize the phenotype

Monitor levels of organic acids, ketones, cholesterol and manage accordingly. Monitor plasma lipoproteins, especially oxidized low density lipoproteins (LDL), small dense LDL and apolipoproteins B.

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