



Patient: **VIKTORIA  
HABANOVA**

DOB: July 04, 1984

Sex: F

MRN: B000109762

**Order Number: U6190091**

Reported: July 04, 2025 15:25

Received: June 20, 2025 10:00

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Bird & Bees

Kathleen Boyd

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London, SW15 1DT

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**3534 Methylation Panel - Plasma & Whole Blood**

**Interpretation At-a-Glance**

**Methylation**

SAM ▼  
Methionine ▼  
Choline ▼  
DMG ▼  
Sarcosine ▼



**Genetic Polymorphism**

**DOWNREGULATING SNPS**

**MTHFR**

C677T — —

A1298C — +

**COMT**

V158M — —

**MTRR**

A66G — +

**MAT1A**

D18777A — —

**SHMT1**

C1240T — +

**UPREGULATING SNPS**

**MTR**

A2756G — +

**CBS**

C699T — —

**BHMT**

G742A + +

**GNMT**

C1289T — +

**Transsulfuration**

Glutathione ▼  
Taurine ▼  
Cysteine ▼  
Serine ▲



**Methylation Status**

**SAM/SAH Ratio**

Low

High

**Methylation Balance**

Un-methylated  
Metabolites

Methyl Group  
Donors

**Met/Sulf Balance**

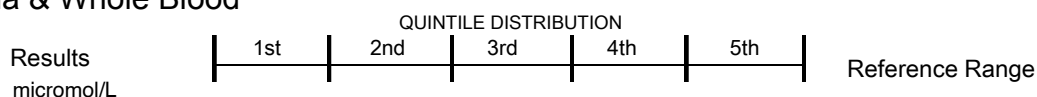
Transsulfuration

Methylation



## 3534 Methylation Panel - Plasma & Whole Blood

Methodology: LCMSMS & Colorimetric



### Methylation Capacity

#### Ratios

1. Methylation Index (SAM/SAH Ratio)	3.3		2.2-6.4
2. Methylation Balance Ratio	1.16		1.03-1.20
3. Met/Sulf Balance Ratio	0.58		0.55-0.64
4. Betaine/Choline Ratio	5.4		2.6-7.7

#### Methyl Group Donors

5. S-adenosylmethionine (SAM)	85		65-150 nanomol/L
6. Methionine	21 <span style="color: red;">L</span>		23-38
7. Choline	7.0		5.2-13.0
8. Betaine	38		21-71
9. Serine	174 <span style="color: red;">H</span>		91-161

#### Methyl Group Metabolites

10. S-adenosylhomocysteine (SAH)	26		16-41 nanomol/L
11. Homocysteine †	6.0		3.7-10.4
12. Dimethylglycine (DMG)	2.0		1.6-5.0
13. Sarcosine	4,193		3,670-6,743 nanomol/L
14. Glycine	305		181-440

#### Transsulfuration Metabolites

15. Cystathionine	128		74-369 nanomol/L
16. Cyst(e)ine	288		271-392
17. Taurine	61		50-139
18. Glutathione †	935		>=669

†These results are not represented by quintile values.

The reference ranges for the Methylation Panel are based on an adult population.

The performance characteristics of all assays have been verified by Genova Diagnostics, Inc. Unless otherwise noted with ♦, the assay has not been cleared by the U.S. Food and Drug Administration.

For more information regarding Methylation clinical interpretation, please refer to the Methylation Panel Support Guide at <https://www.gdx.net/core/support-guides/methylation-support-guide.pdf>



**3535 Add-on Methylation Genomics - Buccal sample**

Methodology: DNA Sequencing

BHMT G742A		Betaine-homocysteine S-methyltransferase	
Your Genotype:		Betaine-homocysteine methyltransferase (BHMT) is the enzyme responsible for remethylation of homocysteine via an alternate pathway using betaine as a methyl donor. <sup>5</sup> BHMT acts as a backup pathway to maintain SAM levels and is expressed primarily in the liver and kidney. <sup>6</sup>	
Allele 1	Allele 2	<h3>Health Implications</h3> <ul style="list-style-type: none"><li>• The BHMT G742A polymorphism results in increased BHMT activity (also referred to as “upregulation”). Upregulation of BHMT may lead to lower levels of homocysteine as well as less dependency on folate and vitamin B-12 as methyl donors.</li><li>• Because this BHMT polymorphism results in increased activity, research suggests that this SNP is protective against many of the clinical conditions related to elevated homocysteine and folate deficiency.</li><li>• This G742A SNP has been associated with reduced all-cause mortality in breast cancer and decreased birth defect risk in some studies.<sup>1-4</sup></li><li>• However, the overuse of choline as a substrate for methylation may have a negative metabolic consequence, because choline is needed for many other processes in the body.<ul style="list-style-type: none"><li>◦ For example, SNPs for this enzyme may result in decreased choline availability for the PEMT pathway, which is responsible for acetylcholine and phospholipid synthesis.<sup>5</sup></li></ul></li><li>• Abnormal choline metabolism may be associated with congenital abnormalities such as Down syndrome and neural tube defects.<sup>7</sup> These risks may be exacerbated by homozygous positive findings combined with low folate intake.</li></ul>	
A	A		
Variant +	Variant +		
Potential Impact: <b>Upregulation</b>			
Genotypes	Amino Acid	<h3>Clinical Considerations</h3> <ul style="list-style-type: none"><li>• Check choline and betaine levels; consider supplementation if applicable. Ensure adequate dietary choline intake.</li><li>• Assess likelihood of zinc insufficiency; evaluate plasma zinc and zinc/copper ratio.</li><li>• Assess SAM/SAH ratio and Methyl Balance Ratio to rule out excessive SAM production.</li></ul>	
GG	Arg Arg		
GA	Arg Gln		
AA	Gln Gln		
Amino Acid Position: 239		<h3>References</h3> <ol style="list-style-type: none"><li>1. Boyles AL, et al. <i>Environ Health Perspect.</i> 2006;114(10):1547-1552.</li><li>2. Shaw GM, et al. <i>BMC Med Gen.</i> 2009;10:49.</li><li>3. Mostowska A, et al. <i>J Med Gen.</i> 2010;47(12):809-815.</li><li>4. da Costa KA, et al. <i>FASEB J.</i> 2014;28(7):2970-2978.</li><li>5. Obeid R. <i>Nutrients.</i> 2013;5(9):3481.</li><li>6. Sunden SL, et al. <i>Arch Biochem Biophys.</i> 1997;345(1):171-174.</li><li>7. Jaiswal SK, et al. <i>Eur J Clin Nutr.</i> 2017;71(1):45-50.</li></ol>	
<b>Arginine to Glutamine</b>			
CGA → CAA			
DNA Position: 821			
<div><div>SNP</div><div>GAGGCTGCC<b>C(G or A)</b>CTGAAAGCT</div><div>Amino Acid Codon</div></div>			
Rs Number: rs3733890			
Location: Chromosome 5q14.1			
<b>* Frequency:</b>			
Population Category	GG	GA	AA
EUR	48%	41%	11%
EAS	52%	41%	7%
AFR	55%	41%	4%
AMR	32%	52%	16%
SAS	52%	43%	5%

\*Population frequency data is from 1000 GENOMES project as sourced from NCBI dbSNP. The population categories are listed below:

**EUR (European):** Americans with Northern and Western European Ancestry, Toscani, Finnish, British, Spanish**EAS (East Asian):** Han Chinese (Beijing), Japanese (Tokyo), Southern Han Chinese, Chinese Dai, Kinh (Vietnam)**AFR (African):** Nigerian, Kenyan, Gambian, Mendi (Sierra Leone), African American, African Caribbean**AMR (Ad Mixed American):** Mexican, Puerto Rican, Colombian, Peruvian**SAS (South Asian):** Americans of Gujarati descent (India), Punjabi (Pakistan), Bengali (Bangladesh), Sri Lankan/Indian in UK

**3535 Add-on Methylation Genomics - Buccal sample**

Methodology: DNA Sequencing

CBS C699T		Cystathionine beta-synthase	
Your Genotype:		Cystathionine beta-synthase (CBS) is the enzyme responsible for homocysteine's irreversible conversion to cystathionine. This is the first step in the transsulfuration pathway that ultimately leads to glutathione production.	
Allele 1	Allele 2		
C	C	<h3>Health Implications</h3> <ul style="list-style-type: none"><li>• The CBS enzyme is strongly regulated by the availability of SAM. Adequate SAM levels leads to an upregulation of the CBS enzyme, allowing homocysteine to be irreversibly committed to the transsulfuration pathway.<sup>1</sup></li><li>• Most literature suggests that CBS C699T polymorphisms result in upregulation of CBS activity favoring transsulfuration and lowering homocysteine.<sup>2,3</sup></li><li>• One study demonstrated the opposite effect in a Chinese population where CBS polymorphisms resulted in increased plasma homocysteine.<sup>4</sup> Therefore, debate exists regarding the impact of C699T polymorphism on enzyme activity.</li><li>• Despite the lack of agreement on enzyme activity, multiple studies demonstrate clinical associations with the C699T polymorphism. These include:<ul style="list-style-type: none"><li>◦ Reduced risk of lymphoma <sup>5</sup></li><li>◦ Reduced risk of venous disease <sup>6,7</sup></li><li>◦ Protective effects against deep vein thrombosis <sup>6</sup></li><li>◦ Decreased risk of coronary artery disease <sup>8</sup></li></ul></li></ul>	
Wild Type -	Wild Type -		
Potential Impact:			
No Upregulation			
Genotypes	Amino Acid	<h3>Clinical Considerations</h3> <ul style="list-style-type: none"><li>• Since this polymorphism is mostly considered to be protective, evaluate homocysteine levels in patients with “wild-type” (negative) CBS genotypes and address causes of elevated homocysteine.</li><li>• Some clinicians consider CBS polymorphisms to potentially “drain” methylation metabolites into the transsulfuration cycle. Evaluate overall methyl balance ratios and consider methylation support if warranted.</li><li>• Reduce levels of oxidative stress which further upregulate the CBS enzyme.</li><li>• Evaluate other transsulfuration metabolites (taurine, cystathionine, and glutathione) to determine if upregulation of CBS is likely. Assess met/sulf balance ratio.</li><li>• Ensure adequate supply of vitamin B-6 and iron, as these are cofactors for the CBS enzyme.</li></ul>	
CC	Tyr Tyr		
CT	Tyr Tyr		
TT	Tyr Tyr		
Amino Acid Position: 233		<h3>References</h3> <ol style="list-style-type: none"><li>1. Stabler SP, et al. <i>Blood</i>. 1993;81(12):3404-3413.</li><li>2. DeStefano Vea. <i>Ann Hum Genet</i>. 1998;62(6):481-490.</li><li>3. Aras Ö, et al. <i>Clin Genet</i>. 2000;58(6):455-459.</li><li>4. Wu X, et al. <i>Hered Cancer Clin Pract</i>. 2014;12(1):2.</li><li>5. Li Q, et al. <i>Cancer Causes Control : CCC</i>. 2013;24(10):1875-1884.</li><li>6. Ayala C, et al. <i>Biomedica</i>. 2010;30(2):259-267.</li><li>7. Hendrix P, et al. <i>J Neurosurg</i>. 2017:1-7.</li><li>8. Kruger WD, et al. <i>Mol Genet Metab</i>. 2000;70(1):53-60.</li></ol>	
Tyrosine to Tyrosine			
TAC → TAT			
DNA Position: 944			
<div><div>SNP</div><div>TGGCTCACTA(C or T)GACACCACCG</div><div>Amino Acid Codon</div></div>			
Rs Number: rs234706			
Location: Chromosome 21q22.3			
* Frequency:			
Population Category	CC	CT	TT
EUR	42%	48%	10%
EAS	95%	5%	<1%
AFR	59%	33%	8%
AMR	72%	25%	3%
SAS	44%	46%	10%

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**3535 Add-on Methylation Genomics - Buccal sample**

Methodology: DNA Sequencing

GNMT C1289T		Glycine N-methyltransferase	
Your Genotype:		Glycine n-methyltransferase (GNMT) is an enzyme that plays a critical role in the disposal of excess s-adenosylmethionine (SAM), which is the body's main methyl donor. GNMT removes methyl groups from SAM by conjugating them with glycine to form the byproduct sarcosine.	
Allele 1	Allele 2		
C	T		
Wild Type - Variant +		<h3>Health Implications</h3> <ul style="list-style-type: none"><li>GNMT acts as a SAM/SAH buffer by disposing excess SAM through conjugation with glycine. This process is downregulated in response to low 5-MTHF and SAM levels. Increased GNMT activity could potentially lead to increased sarcosine levels, which has been associated with prostate cancer risk in several studies.<sup>1-3</sup><ul style="list-style-type: none"><li>However, in one study of Taiwanese men (where GNMT polymorphism is less common), GNMT polymorphism showed a protective effect on prostate cancer risk, which highlights the differences in SNP frequencies in different populations.<sup>4</sup></li></ul></li><li>The C1289T polymorphism results in upregulation of the GNMT enzyme which increases the rate of SAM disposal and sarcosine creation. This may limit SAM availability for methylation reactions and reduce its regulatory effects on the transsulfuration and/or folate pathways.</li><li>GNMT is also involved in detoxification and antioxidant pathways. This may play a role in the increased cancer risk demonstrated in homozygous negative individuals and in animal models.</li><li>GNMT SNPs have been shown to play a role in elevating plasma homocysteine, particularly with folate-restriction.<sup>5</sup></li></ul>	
Potential Impact:			
Upregulation			
Genotypes	Amino Acid		
<div>CC</div> <div>CT</div> <div>TT</div>	Non-Coding Non-Coding Non-Coding		
Amino Acid Position: Untranslated Region			
DNA Position: 4962		<h3>Clinical Considerations</h3> <ul style="list-style-type: none"><li>Evaluate methylation balance, SAM/SAH, and sarcosine levels.</li><li>Ensure adequate levels of glycine, as this is a substrate for the reaction catalyzed by GNMT and is also involved in glutathione synthesis.</li></ul>	
SNP			
AGTGCTTATG (C or T) TTTAAGTGCG			
Rs Number: rs10948059			
Location: Chromosome 6p21.1			
* Frequency:			
Population Category	CC	CT	TT
EUR	29%	47%	24%
EAS	70%	28%	2%
AFR	23%	43%	34%
AMR	50%	44%	6%
SAS	36%	47%	17%
<h3>References</h3> <ol style="list-style-type: none"><li>Lucarelli G, et al. <i>Prostate</i>. 2012;72(15):1611-1621.</li><li>Jentzmik F, et al. <i>Eur Urol</i>. 2010;58(1):12-18.</li><li>Sreekumar A, et al. <i>Nature</i>. 2009;457(7231):910.</li><li>Chen M, et al. <i>PloS one</i>. 2014;9(5):e94683.</li><li>Beagle B, et al. <i>J Nutr</i>. 2005;135(12):2780-2785.</li></ol>			

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## 3535 Add-on Methylation Genomics - Buccal sample

Methodology: DNA Sequencing

MAT1A D18777A		Methionine adenosyltransferase	
Your Genotype:		<p>Methionine adenosyltransferase (MAT) is the enzyme that catalyzes the conversion of methionine into the body's main methyl donor, s-adenosylmethionine (SAM). This enzyme requires magnesium as a cofactor and is downregulated by oxidative stress, such as alcohol and free radical damage.</p> <h3>Health Implications</h3> <ul style="list-style-type: none"><li>Methionine adenosyltransferase (MAT) activity is critical to methylation. There are a few MAT1A genetic polymorphisms studied that lead to MAT1A deficiency (also known as Mudd's Disease), but this condition is extremely rare.</li><li>The D18777A SNP is fairly common in the human population and has associations with cardiovascular disease risk.<sup>1</sup></li><li>Although literature is scant on this mutation, some studies have demonstrated higher homocysteine levels with this polymorphism.<sup>2</sup> Another study also demonstrated that this correlation was modulated by overall dietary fat intake.<sup>3</sup></li><li>Another study demonstrated that the D18777A SNP was associated with higher rates of stroke independent of homocysteine levels, which was hypothesized to be due to methylation activity impairment.<sup>1</sup></li></ul> <h3>Clinical Considerations</h3> <ul style="list-style-type: none"><li>Evaluate methylation balance, SAM/SAH, and sarcosine levels.</li><li>Reduce levels of oxidative stress, such as free radical exposure and alcohol intake as these can further impair the MAT1A enzyme.</li><li>Ensure adequate levels of MAT1A cofactors such as magnesium and potassium. Consider testing RBC magnesium and potassium.</li><li>Patients with this polymorphism may have higher homocysteine in response to dietary fat intake than those without.<sup>3</sup> Monitor advanced cardiovascular risk markers if clinically appropriate.</li></ul>	
Allele 1	Allele 2		
G	G		
Wild Type -	Wild Type -		
Potential Impact:			
No Downregulation			
Genotypes	Amino Acid		
GG	Non-Coding		
GA	Non-Coding		
AA	Non-Coding		
Amino Acid Position: Untranslated Region			
DNA Position: 23777			
SNP			
GCTTTTCTCT (G or A)TAATGTGTCA			
Rs Number: rs3851059			
Location: Chromosome 10q22.3			
* Frequency:			
Population Category	GG	GA	AA
EUR	50%	43%	7%
EAS	36%	48%	16%
AFR	62%	34%	4%
AMR	52%	40%	8%
SAS	42%	45%	13%
References			
1. Lai CQ, et al. Am J Clin Nutr. 2010;91(5):1377-1386.			
2. Beagle B, et al. J Nutr. 2005;135(12):2780-2785.			
3. Huang T, et al. Nutr Metab Cardiovasc Dis. 2012;22(4):362-368.			

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**3535 Add-on Methylation Genomics - Buccal sample**

Methodology: DNA Sequencing

MTR A2756G		Methionine synthase	
Your Genotype:		Methionine synthase (MS/MTR) is responsible for converting homocysteine back into methionine by using 5-MTHF as a methyl donor. This reaction requires zinc and active B-12 (methylcobalamin) as cofactors and is the main pathway responsible for homocysteine recycling in every cell.	
Allele 1	Allele 2		
A	G	<h3>Health Implications</h3> <ul style="list-style-type: none"><li>• The A2756G polymorphism is the most common MTR SNP discussed in the literature.</li><li>• It is generally accepted that this SNP upregulates the MTR enzyme leading to lower homocysteine levels.<sup>1</sup></li><li>• The impact of this SNP on global DNA methylation is debated in the literature, however clinical associations with the A2756G polymorphism include congenital birth defects such as spina bifida, cleft lip/palate, and cardiac defects.<sup>2-4</sup></li><li>• One hypothesis is that as the MTR enzyme is at the junction between the folate pathway and the methylation pathway, upregulation of MTR may shunt folate groups to the methylation cycle at the expense of other folate needs, such as purine/nucleotide synthesis.</li><li>• Several epidemiological studies on MTR polymorphism have demonstrated risk associations with various cancers, evidence remains controversial.<sup>5-7</sup> Many of these risk associations appear to be population/ethnicity specific, which could be due to gene-gene interactions with MTRR and MTHFR.</li></ul> <h3>Clinical Considerations</h3> <ul style="list-style-type: none"><li>• Compare any MTR polymorphisms with MTHFR and MTRR genetic results.</li><li>• Evaluate homocysteine, SAM/SAH ratio, and monitor biomarkers for vitamin B-12 and folate.</li><li>• Ensure adequate dietary intake of folate and vitamin B-12.</li></ul>	
Wild Type -	Variant +		
Potential Impact:			
Potential Upregulation			
Genotypes	Amino Acid		
AA	Asp Asp		
AG	Asp Gly		
GG	Gly Gly		
Amino Acid Position: 919			
Aspartate to Glycine			
GAC → GGC			
DNA Position: 3179			
ATTAGACAG <b>G(A or G)C</b> CATTATGAG			
Amino Acid Codon			
Rs Number: rs1805087			
Location: Chromosome 1q43			
* Frequency:			
Population Category	AA	AG	GG
EUR	69%	30%	1%
EAS	72%	25%	3%
AFR	47%	42%	11%
AMR	65%	33%	2%
SAS	42%	47%	11%
<h3>References</h3> <ol style="list-style-type: none"><li>1. Ho V, et al. <i>Genes Nutr.</i> 2013;8(6):571-580.</li><li>2. Wang W, et al. <i>Genet Test Mol Biomarkers.</i> 2016;20(6):297-303.</li><li>3. Klerk M, et al. <i>Thromb Res.</i> 2003;110(2-3):87-91.</li><li>4. Doolin MT, et al. <i>Am J Hum Genet.</i> 2002;71(5):1222-1226.</li><li>5. Bleich S, et al. <i>Epigenomics.</i> 2014;6(6):585-591.</li><li>6. Hosseini M. <i>Pol J of Pathol.</i> 2013;64(3):191-195.</li><li>7. Jiang-hua Q, et al. <i>Tumour Biol.</i> 2014;35(12):11895-11901.</li></ol>			

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**3535 Add-on Methylation Genomics - Buccal sample**

Methodology: DNA Sequencing

MTRR A66G		Methionine synthase reductase																									
Your Genotype:		Methionine synthase reductase (MTRR) is an enzyme that works in cooperation with methionine synthase (MTR) by reducing oxidized forms of vitamin B-12 to be reused. This allows MTR to continue to convert homocysteine back into methionine.																									
Allele 1	Allele 2																										
A	G	<h3>Health Implications</h3> <ul style="list-style-type: none"><li>MTRR polymorphisms result in decreased enzyme activity and therefore a decreased capacity to recycle oxidized cobalamin (vitamin B-12). This decreased enzyme activity can affect methylation capacity by limiting the amount of active B-12 available for homocysteine conversion.<sup>1</sup></li><li>Both MTRR polymorphisms can result in homocysteine elevation, independent of folate, B-12, or B-6 levels.<sup>2</sup></li><li>The A66G polymorphism is the most commonly studied MTRR SNP. It has been associated with numerous clinical conditions, such as various cancers, birth defects, metabolic syndrome, mood disorder, and elevated homocysteine.<sup>3-5</sup></li><li>The A66G polymorphism has also been shown to correlate with global DNA hypomethylation, which is a direct marker for methylation impairment.</li></ul> <h3>Clinical Considerations</h3> <ul style="list-style-type: none"><li>Compare any MTRR polymorphisms with MTHFR and MTR genetic results. Evaluate homocysteine, SAM/SAH ratio, and monitor biomarkers for vitamin B-12 and folate.</li><li>Ensure adequate dietary intake of folate and vitamin B-12, consider repletion with methylcobalamin in these individuals.</li><li>Ensure adequate vitamin B-2 and B-3 status, as they are cofactors for the MTRR enzyme.</li><li>Assess antioxidant capacity, as oxidative stress impacts levels of methylcobalamin.</li></ul>																									
Wild Type -	Variant +																										
Potential Impact: <b>Downregulation</b>																											
Genotypes	Amino Acid																										
<div><div>AA</div><div>AG</div><div>GG</div></div>	<div>Ile Ile</div> <div>Ile Met</div> <div>Met Met</div>																										
Amino Acid Position: 22																											
Isoleucine to Methionine																											
ATA → ATG																											
DNA Position: 203																											
<div><div>CAGAAGAA</div><div>AT(A or G)</div><div>TGTGAGCAAG</div></div> <div>SNP</div> <div>Amino Acid Codon</div>																											
Rs Number: rs1801394																											
Location: Chromosome 5p15.31																											
<h3>* Frequency:</h3> <table><tr><th>Population Category</th><th>AA</th><th>AG</th><th>GG</th></tr><tr><td>EUR</td><td>38%</td><td>34%</td><td>28%</td></tr><tr><td>EAS</td><td>54%</td><td>37%</td><td>9%</td></tr><tr><td>AFR</td><td>59%</td><td>36%</td><td>5%</td></tr><tr><td>AMR</td><td>26%</td><td>57%</td><td>17%</td></tr><tr><td>SAS</td><td>N/A</td><td>N/A</td><td>N/A</td></tr></table> <h3>References</h3> <ol style="list-style-type: none"><li>Olteanu H, et al. <i>Biochemistry</i>. 2002;41(45):13378-13385.</li><li>Gaughan DJ, et al. <i>Atherosclerosis</i>. 2001;157(2):451-456.</li><li>Jamerson BD, et al. <i>Int J Geriatr Psychiatry</i>. 2013;28(9):925-932.</li><li>Hassan FM, et al. <i>Gene</i>. 2017;629:59-63.</li><li>Guo QN, et al. <i>BioMed Res Int</i>. 2017;2017:3043476.</li></ol>				Population Category	AA	AG	GG	EUR	38%	34%	28%	EAS	54%	37%	9%	AFR	59%	36%	5%	AMR	26%	57%	17%	SAS	N/A	N/A	N/A
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SAS	N/A	N/A	N/A																								

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**3535 Add-on Methylation Genomics - Buccal sample**

Methodology: DNA Sequencing

**SHMT1 C1240T****Serine hydroxymethyltransferase 1**

Your Genotype:

Allele 1

Allele 2

**C****T**

Wild Type -

Variant +

Potential Impact:

**Downregulation**

Genotypes

C	C
C	T
T	T

Amino Acid

Leu Leu

Leu Phe

Phe Phe

Amino Acid Position: 474

**Leucine to Phenylalanine**

CTC → TTC

DNA Position: 1631

SNP  
↓

CTTCGCTCT (C or T) TC TTCCCTCT

Amino Acid Codon

Rs Number: rs1979277

Location: Chromosome 17p11.2

**Health Implications**

- SHMT1 is a bidirectional enzyme that can create a short-cut for methylation of homocysteine back to methionine through rapid creation of 5-MTHF. However, SHMT generally gives metabolic priority to nucleotide synthesis over SAM synthesis.<sup>1</sup>
- The C1240T polymorphism alters the SHMT1 enzyme function to favor the folate cycle over the methylation cycle to an even greater extent. Ultimately, this imbalance can cause reduced circulating folate (5-MTHF) levels and increased homocysteine.<sup>2</sup>
- This SNP adversely affects DNA synthesis, methylation systems, and causes genome instability. It eventually leads to oncogene overexpression and tumor suppressor gene inactivation.<sup>1,3</sup>
- The C1240T SNP has been associated with several clinical conditions, including various cancers and exacerbation of cardiovascular disease risk associated with MTHFR.<sup>4-6</sup>

**Clinical Considerations**

- Evaluate MTHFR SNP which may exacerbate CVD risk and low folate status.
- Consider supplementation with 5-MTHF and other methyl donors if high homocysteine or low SAM/SAH ratio.
- Consider additional B-vitamin supplementation to support MTHFR enzyme, such as vitamins B-2, B-3, and B-12.

**\* Frequency:**

Population Category	CC	CT	TT
EUR	45%	43%	12%
EAS	87%	13%	<1%
AFR	33%	47%	20%
AMR	59%	41%	<1%
SAS	N/A	N/A	N/A

**References**

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**3535 Add-on Methylation Genomics - Buccal sample**

Methodology: DNA Sequencing

MTHFR C677T		5,10-methylenetetrahydrofolate reductase	
Your Genotype:		<p>Methylenetetrahydrofolate reductase (MTHFR) is a key regulatory enzyme which converts 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate (5-MTHF). This step activates folate to be used for homocysteine (Hcy) conversion to methionine, instead of nucleotide synthesis.</p> <h3>Health Implications</h3> <ul style="list-style-type: none"><li>• The C677T polymorphism downregulates enzymatic activity, which can limit methylation reactions in the body. The C677T polymorphism results in an increased risk of high homocysteine and an increased tendency for lower folate levels.<sup>1,2</sup></li><li>• Homozygosity for 677 (+/+) results in 60-70% reduction in MTHFR enzyme activity. Heterozygosity for 677 (-/+) results in 30-40% reduction in MTHFR enzyme activity.<sup>3</sup></li><li>• Lower levels of B-vitamin and folate increase the risk of elevated homocysteine related to MTHFR SNPs.<sup>2</sup></li><li>• Homozygous C677T subjects have higher Hcy levels, while heterozygous subjects have mildly raised Hcy levels compared to controls.<sup>4</sup></li><li>• MTHFR C677T SNPs have been associated with many disease processes including:<ul style="list-style-type: none"><li>◦ Cardiovascular disease <sup>5-7</sup></li><li>◦ Depression and schizophrenia <sup>8,9</sup></li><li>◦ Increased risk of birth defects and Down’s syndrome <sup>10</sup></li><li>◦ Psoriasis</li><li>◦ Diabetes</li><li>◦ Parkinson’s disease</li><li>◦ Various cancers <sup>4</sup></li></ul></li></ul> <h3>Clinical Considerations</h3> <ul style="list-style-type: none"><li>• Ensure adequate intake of dark-green leafy vegetables and other B vitamin-rich foods.</li><li>• Evaluate homocysteine, SAM, and SAH levels.</li><li>• Supplementation with methylated folate and folate-rich foods may help lower Hcy and mitigate risk.<sup>11</sup></li><li>• Evaluate the status of vitamin B-2 and B-3 (MTHFR enzyme cofactors).</li></ul> <h3>References</h3> <ol style="list-style-type: none"><li>1. Yang Q, et al. <i>Am J Clin Nutr</i>. 2012;95(5):1245-1253.</li><li>2. Garcia-Minguillan CJ, et al. <i>Genes Nutr</i>. 2014;9(6):435.</li><li>3. Weisberg IS, et al. <i>Atherosclerosis</i>. 2001;156(2):409-415.</li><li>4. Liew S-C, et al. <i>Eur J Med Genet</i>. 2015;58(1):1-10.</li><li>5. Zhang P, et al. <i>Angiology</i>. 2015;66(5):422-432.</li><li>6. Yang KM, et al. <i>Biomed Rep</i>. 2014;2(5):699-708.</li><li>7. Cui T. <i>Int J Neurosci</i>. 2015.</li><li>8. Wu YL, et al. <i>Prog Neuropsychopharmacol Biol Psychiatry</i>. 2013;46:78-85.</li><li>9. Hu CY, et al. <i>J Neural Transm (Vienna)</i>. 2015;122(2):307-320.</li><li>10. Yadav U, et al. <i>Metab Brain Dis</i>. 2015;30(1):7-24.</li><li>11. Zhao M, et al. <i>Stroke</i>. 2017;48(5):1183-1190.</li></ol>	
Allele 1	Allele 2		
C	C		
Wild Type - Wild Type -			
Potential Impact:			
No Downregulation			
Genotypes	Amino Acid		
CC	Ala Ala		
CT	Ala Val		
TT	Val Val		
Amino Acid Position: 222			
Alanine to Valine			
GCC → GTC			
DNA Position: 894			
SNP			
TCTGCGGGA G(C or T)C GATTTCATC			
Amino Acid Codon			
Rs Number: rs1801133			
Location: Chromosome 1p36.22			
* Frequency:			
Population Category	CC	CT	TT
EUR	47%	44%	9%
EAS	37%	47%	16%
AFR	81%	19%	<1%
AMR	32%	52%	16%
SAS	68%	30%	2%

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**3535 Add-on Methylation Genomics - Buccal sample**

Methodology: DNA Sequencing

MTHFR A1298C		5,10-methylenetetrahydrofolate reductase	
Your Genotype:		Methylenetetrahydrofolate reductase (MTHFR) is a key regulatory enzyme which converts 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate (5-MTHF). This step activates folate to be used for homocysteine conversion to methionine, instead of nucleotide synthesis.	
Allele 1	Allele 2		
A	C		
Wild Type - Variant +			
Potential Impact:			
No Downregulation			
Genotypes		Amino Acid	
AA		Glu Glu	
AC		Glu Ala	
CC		Ala Ala	
Amino Acid Position: 429			
Glutamate to Alanine			
GAA → GCA			
DNA Position: 1515			
SNP			
ACCAAGTGAA G(A or C)AAGTGTCTTT			
Amino Acid Codon			
Rs Number: rs1801131			
Location: Chromosome 1p36.22			
* Frequency:			
Population Category	AA	AC	CC
EUR	43%	45%	12%
EAS	63%	33%	4%
AFR	78%	21%	1%
AMR	62%	34%	4%
SAS	39%	44%	17%
Health Implications			
• The A1298C homozygous SNP mutation downregulates enzyme activity but may not independently affect folate or homocysteine levels. <sup>1</sup> However, a combined heterozygosity for both 677T and 1298C mutations does result in significant plasma homocysteine elevation. <sup>1,2</sup>			
• Heterozygosity for only 1298 (-/+) has not been shown to affect overall MTHFR enzyme activity, however, homozygosity for 1298 (+/+) results in 30-40% reduction in MTHFR enzyme activity. <sup>3</sup>			
• MTHFR A1298C SNPs have been associated with many disease processes including:			
◦ Cardiovascular disease <sup>4-6</sup>			
◦ Male infertility <sup>7,8</sup>			
◦ Increased risk of birth defects <sup>9</sup>			
◦ Certain cancer types <sup>10-12</sup>			
Clinical Considerations			
• Ensure adequate intake of dark-green leafy vegetables and other B vitamin-rich foods.			
• Evaluate homocysteine, SAM, and SAH levels.			
• Supplementation with methylated folate and folate-rich foods may help lower Hcy and mitigate risk. <sup>13</sup>			
• Evaluate the status of vitamin B-2 and B-3 (MTHFR enzyme cofactors).			
References			
1. Isotalo PA, et al. <i>Am J Hum Genet</i> . 2000;67(4):986-990.			
2. van der Put NM, et al. <i>Am J Hum Genet</i> . 1998;62(5):1044-1051.			
3. Weisberg IS, et al. <i>Atherosclerosis</i> . 2001;156(2):409-415.			
4. Kang S, et al. <i>J Clin Neurosci</i> . 2014;21(2):198-202.			
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13. Zhao M, et al. <i>Stroke</i> . 2017;48(5):1183-1190.			

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**3535 Add-on Methylation Genomics - Buccal sample**

Methodology: DNA Sequencing

COMT V158M		Catechol-O-methyltransferase	
Your Genotype:		Catechol-O-Methyltransferase (COMT) is a key enzyme involved in the deactivation of catechol compounds, including catecholamines, catechol estrogens, catechol drugs such as L-DOPA, and various chemicals and toxins such as aryl hydrocarbons.	
Allele 1	Allele 2		
G	G	<b>Health Implications</b> <ul style="list-style-type: none"><li>• COMT polymorphisms result in decreased enzyme activity. Individuals with COMT SNPs may have an increased risk of inefficient methylation of catecholamines, estrogens, and toxins.<sup>1,2</sup></li><li>• The most common genotype of COMT in most populations is heterozygous (+/-). Individuals with a homozygous positive (+/+) genotype for COMT have a 3-4-fold reduction in COMT activity.</li><li>• COMT polymorphisms have been implicated in mood disturbances such as anxiety, panic disorder, eating disorder, aggressiveness, anger, alcoholism, and severity of bipolar disorder.<sup>3-5</sup></li><li>• COMT polymorphism has been implicated in risk of breast cancer, particularly in women with prolonged estrogen exposure;<sup>6,7</sup> or in women with low folate and high homocysteine.<sup>8</sup> Also, COMT SNPs have been shown to correlate with higher estrogen levels with estrogen replacement therapy.<sup>9</sup></li><li>• Fibromyalgia and migraine have been associated with COMT polymorphisms as well.<sup>10,11</sup></li></ul>	
Wild Type -	Wild Type -		
Potential Impact:		<b>Clinical Considerations</b> <ul style="list-style-type: none"><li>• Evaluate methylation pathway to locate any potential backup.</li><li>• Ensure adequate B6, B12, folate, magnesium, betaine, and methionine to ensure adequate SAM production.</li><li>• SAM-e supplementation may be considered, as it is the cofactor for COMT, however, this therapy is contraindicated in bipolar disorder.</li><li>• Minimize stress, since catecholamine levels may already be high.</li><li>• Make sure to appropriately monitor estrogen levels and estrogen metabolites, especially if your patient is on estrogen replacement therapy.</li><li>• Consider additional antioxidant support, especially if low levels of glutathione are reported.</li></ul>	
<b>No Downregulation</b>			
Genotypes	Amino Acid	<b>References</b> <ol style="list-style-type: none"><li>1. Lachman et al. <i>Pharmacogenetics</i>. 1996;6(3):243-250.</li><li>2. Mannisto et al. <i>Pharmacol Rev</i>. 1999;51(4):593-628.</li><li>3. Woo JM, et al. <i>Am J Psychol</i>. 2002;159(10):1785-1787.</li><li>4. Rujescu D, et al. <i>Biol Psychiatry</i>. 2003;54(1):34-39.</li><li>5. Papolos DF, et al. <i>Mol Psychiatry</i>. 1998;3(4):346-349.</li><li>6. Huang CS, et al. <i>Cancer Res</i>. 1999;59(19):4870-4875.</li><li>7. Lavigne JA, et al. <i>Cancer Res</i>. 1997;57(24):5493-5497.</li><li>8. Goodman JE, et al. <i>Carcinogenesis</i>. 2001;22(10):1661-1665.</li><li>9. Worda C, et al. <i>Hum Reprod</i>. 2003;18(2):262-266.</li><li>10. Gursoy S, et al. <i>RheumatolInt</i>. 2003;23(3):104-107.</li><li>11. Emin Erdal M, et al. <i>Brain Res Mol Brain Res</i>. 2001;94(1-2):193-196.</li></ol>	
<div><div>GG</div><div>GA</div><div>AA</div></div>	<div>Val Val</div> <div>Val Met</div> <div>Met Met</div>		
Amino Acid Position: 158			
Valine to Methionine			
GTG →ATG			
DNA Position: 721			
<div><div>SNP</div><div>TTTCGCTGGC (G or A)TG AAGGACAA</div><div>Amino Acid Codon</div></div>			
Rs Number: rs4680			
Location: Chromosome 38.p12			
<b>* Frequency:</b>			
Population Category	GG	GA	AA
EUR	22%	53%	25%
EAS	43%	47%	10%
AFR	46%	45%	9%
AMR	54%	37%	8%
SAS	37%	41%	22%

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**3535 Add-on Methylation Genomics - Buccal sample****Commentary**

This test has been developed and its performance characteristics determined by Genova Diagnostics, Inc. It has not been cleared by the U.S. Food and Drug Administration.

Commentary is provided to the practitioner for educational purposes, and should not be interpreted as diagnostic or treatment recommendations. Diagnosis and treatment decisions are the responsibility of the practitioner.

The accuracy of genetic testing is not 100%. Results of genetic tests should be taken in the context of clinical representation and familial risk. The prevalence and significance of some allelic variations may be population specific.

Any positive findings in your patient's test indicate genetic predisposition that could affect physiologic function and risk of disease. We do not measure every possible genetic variation. Your patient may have additional risk that is not measured by this test. Negative findings do not imply that your patient is risk-free.

DNA sequencing is used to detect polymorphisms in the patient's DNA sample. The sensitivity and specificity of this assay is <100%.