VibrantWellness

Methylation Panel

Interpretive Guide

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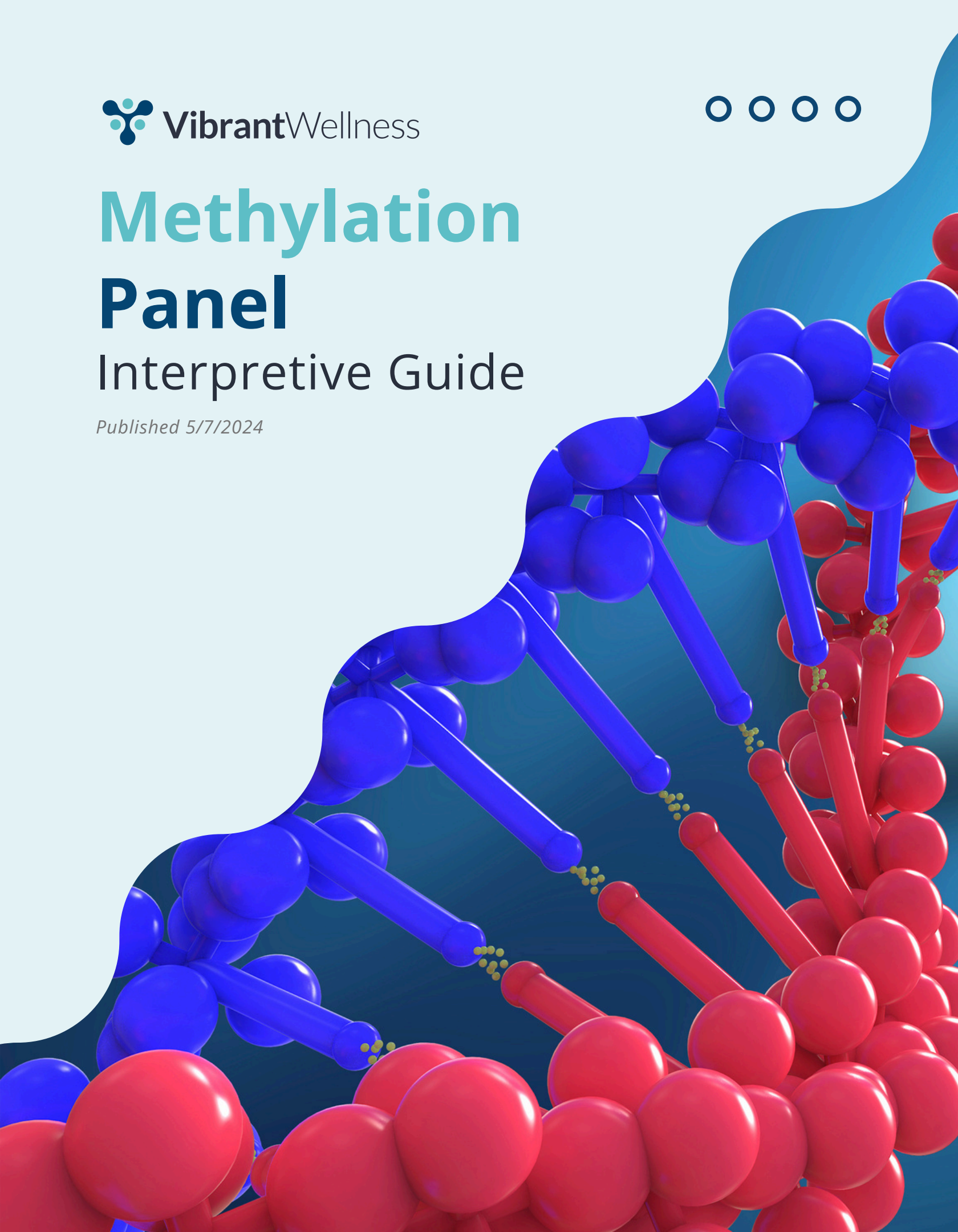

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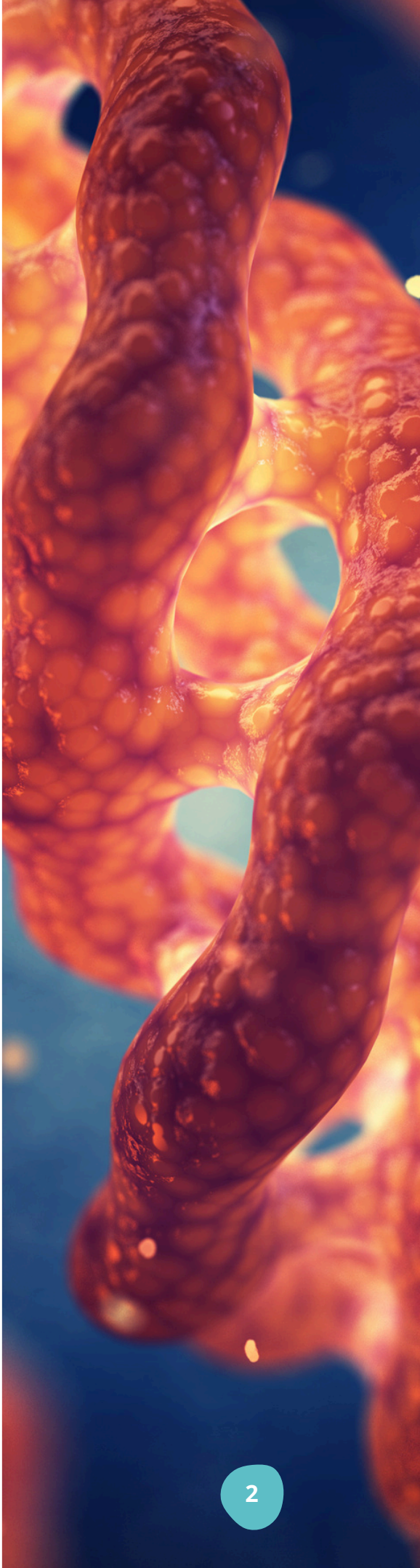
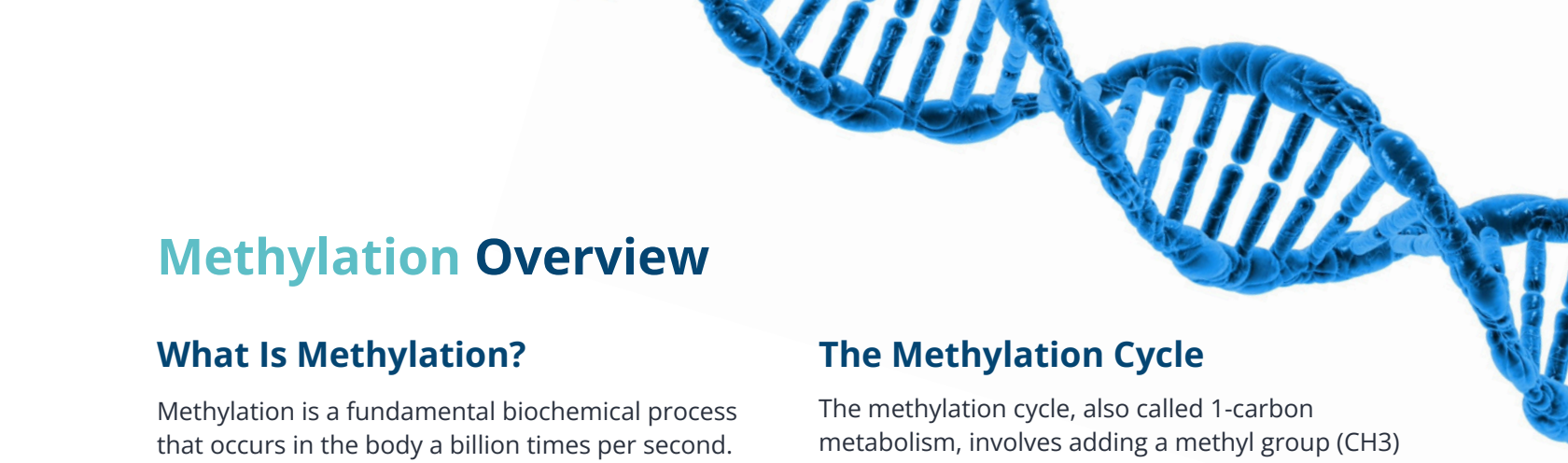




Methylation Overview

What Is Methylation?

Methylation is a fundamental biochemical process that occurs in the body a billion times per second. It aids in processing nutrients and molecules to support various body systems and plays a crucial role in gene regulation.

Methylation is imperative to many biochemical processes in the body, including:

- Hormone, heavy metal, and chemical detoxification
- Nitric oxide production and vascular health
- Neurotransmitter metabolism
- Histamine metabolism
- Glutathione production
- DNA and RNA synthesis
- Cell membrane repair
- Immunomodulation
- ATP synthesis
- Myelination
- Epigenetic modification
- And more

DNA Methylation

DNA methylation is one of biology's most widely studied forms of methylation. While your DNA never changes, your genes can be regulated (turned “on” or “off”) via epigenetic processes. These epigenetic processes include histone modification, non-coding RNA, and methylation.

In DNA methylation, a methyl group is added to the carbon atom of a cytosine nucleotide, forming 5-methylcytosine (5mC). This process primarily occurs at cytosine-guanine (CpG) dinucleotides, where a guanine nucleotide follows a cytosine nucleotide.

Methylation is generally associated with "switching off" or inhibiting a gene, while demethylation is associated with “switching on” or activating a gene.

The Methylation Cycle

The methylation cycle, also called 1-carbon metabolism, involves adding a methyl group (CH3) to a molecule and then recycling methyl donors so they can be used again and again.

Key components of the methylation cycle include:

- **Methyl Donors:** Methyl groups are transferred from methyl donor molecules to acceptor molecules. Common methyl donors include s-adenosylmethionine (SAMe), 5-methyltetrahydrofolate (folate), methylcobalamin (vitamin B12), and trimethylglycine (TMG).
- **Methyltransferase Enzymes:** These enzymes facilitate the transfer of methyl groups from methyl donors to specific target molecules, such as DNA, RNA, proteins, or small molecules.
- **Regeneration of Methyl Donors:** After donating a methyl group, methyl donors must be recycled before they can be used again. For example, S-adenosylmethionine (SAM or SAMe) is converted into S-adenosylhomocysteine (SAH) after transferring a methyl group, also called “demethylation.” SAH is then hydrolyzed to homocysteine, which can be remethylated to regenerate SAM. The remethylation of homocysteine can occur through several pathways, including the folate and methionine cycles.
- **Interplay with Folate and Vitamin B12:** The methylation cycle is closely linked to folate and vitamin B12 metabolism. Folate (as 5-methyltetrahydrofolate) acts as a carrier of one-carbon units, while vitamin B12 is required to convert homocysteine to methionine, a precursor of SAM.
- **Regulation of Gene Expression:** Methylation of DNA and histone proteins plays a crucial role in regulating gene expression. Alterations in methylation patterns can influence gene activity and cellular function.

Why Order the Methylation Panel?

Methylation pathways significantly overlap with virtually all organ systems and metabolic functions in the human body and can impact health, energy, detoxification, emotional and psychological function, and cognition.

Essential nutrients—including folate and vitamin B12—play a role in methylation. Without optimal levels of these nutrients in the correct form, methylation can become impaired and dysfunctional, leading to illness and disease and affecting quality of life. Similarly, a genetic abnormality of one or more genes related to methylation can cause methylation cycles to become dysfunctional.

The Vibrant Methylation panel measures vital nutrients required for methylation and genetic variations impacting the methylation cycle. In this way, the Methylation Panel assesses individual genetic predispositions to nutritional deficiency, folate and methionine cycle dysfunction, and current methylation status so you can recommend effective and appropriate dietary and lifestyle changes to help your patients optimize methylation.

Clinical Utility

Functional Methylation Biomarkers + Genetic SNPs = Increased Value
The SNPs measured on the Methylation Panel represent your patient's genotype, a measurable expression of their genetic SNPs, and provide insight into individual predisposition for impaired enzyme function. By also measuring the functional methylation biomarkers, vitamin B12, folate, and homocysteine, the Methylation Panel also assesses the phenotypic expression of genotypes. A phenotype refers to an organism's observable characteristics or traits resulting from the interaction between its genetic makeup (genotype) and the environment. The combination of genetic predisposition and functional methylation biomarkers allows you to tailor treatment plans unique to your clients.

How To Use SNPs To Influence Outcomes
Methylation processes require many nutrient cofactors, including dietary amino acids, minerals, and vitamins. While the Methylation Panel identifies possible metabolic inefficiencies and downstream effects (e.g., elevated homocysteine), it can also be used to design targeted treatment plans using simple whole foods and supplementation when necessary to support the optimal function of these pathways.

The Complexities of SAM
SAM is necessary for most methylation reactions throughout the body. Once SAM donates its methyl group, it becomes SAH, which reversibly converts into homocysteine. SAH inhibition of methyltransferases ties up methyl groups, inhibiting global methylation. Research suggests SAH is a more sensitive marker of poor methylation status, cardiovascular disease risk, and Alzheimer's disease risk than homocysteine.[1] [2] Fortunately, homocysteine is routinely shuttled out of the cell. This continuous conversion of SAH to homocysteine allows the recycling of homocysteine back to methionine for continued methylation support. ***Note: homocysteine serves a vital purpose as it feeds into the transsulfuration, which is necessary for glutathione production.***

Methylation Panel Analytes

The Methylation Panel identifies genetic variants impacting the methylation cycle and measures functional methylation biomarkers.

Methylation Genetics

The Methylation Panel assesses ten single-nucleotide polymorphisms (SNPs) that impact the methylation cycle, including the folate cycle and methionine recycling.

- See Table 2 for a quick reference guide that provides SNP names, rsIDs, enzyme functions, and genotypes.
- See Table 3 for clinical implications and nutrition and supplement management options.

Functional Methylation Biomarkers

The Methylation Panel includes three functional methylation biomarkers.

Vitamin B12
Methionine synthase is a vitamin B12-dependent enzyme in the remethylation process. Specifically, methionine synthase uses vitamin B12 and active folate (5-methyltetrahydrofolate, 5-MTHF) to convert homocysteine to methionine.

Folate (vitamin B9)
In the methylation pathway, active folate (5-MTHF) supplies a methyl group to convert homocysteine to methionine, which is then converted to the universal methyl donor, SAM. Although nutrients other than folate supply or transport methyl groups (methionine, choline, and vitamin B12), only folate is capable of de novo generation of one carbon groups. As a result, folate is crucial in the methylation pathway. Thus, folate deficiency can detrimentally affect the methylation pathway, giving rise to various clinical conditions.[3] [4]

Homocysteine
Elevated homocysteine is associated with poor overall methylation status. Homocysteine is a naturally occurring amino acid produced during the methylation process. Two routes maintain the concentrations of homocysteine:

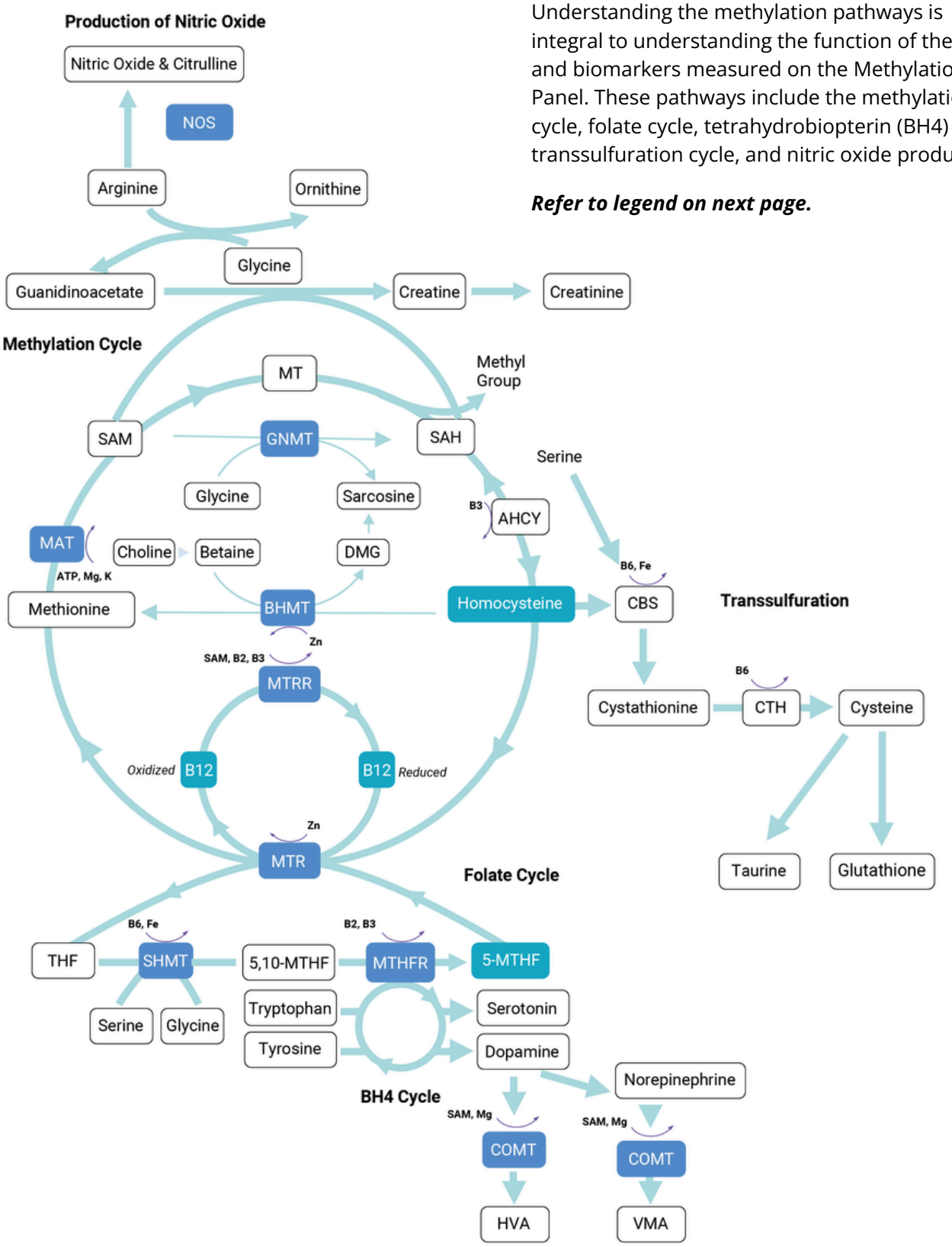
1. The remethylation pathway, where homocysteine is converted back to methionine.
2. The transsulfuration pathway, where homocysteine is converted to cystathionine to form cysteine.

Thus, altered gene activity in any given pathway can affect these processes, resulting in altered levels of homocysteine in the blood. Elevated plasma homocysteine is a risk factor for cardiovascular disease and Alzheimer's disease. Additionally, the reactions that remove homocysteine are very sensitive to B vitamin status, including B12, B6, and folate, as these vitamins are required to break down homocysteine.

*Serum folate and B12 are the two most important methyl donors, followed by betaine (a.k.a. trimethylglycine) and choline.

Interpreting the Methylation Panel

Methylation Pathways with Cofactors



Methylation Pathways Overview

Understanding the methylation pathways is integral to understanding the function of the SNPs and biomarkers measured on the Methylation Panel. These pathways include the methylation cycle, folate cycle, tetrahydrobiopterin (BH4) cycle, transsulfuration cycle, and nitric oxide production.

Refer to legend on next page.

Methylation Pathways with Cofactors *(Legend)*

Key

Cofactors	Zn
Primary Pathway	
Secondary Pathway	
Measured Gene	MAT
Measured Biomarker	B12

Biomarkers

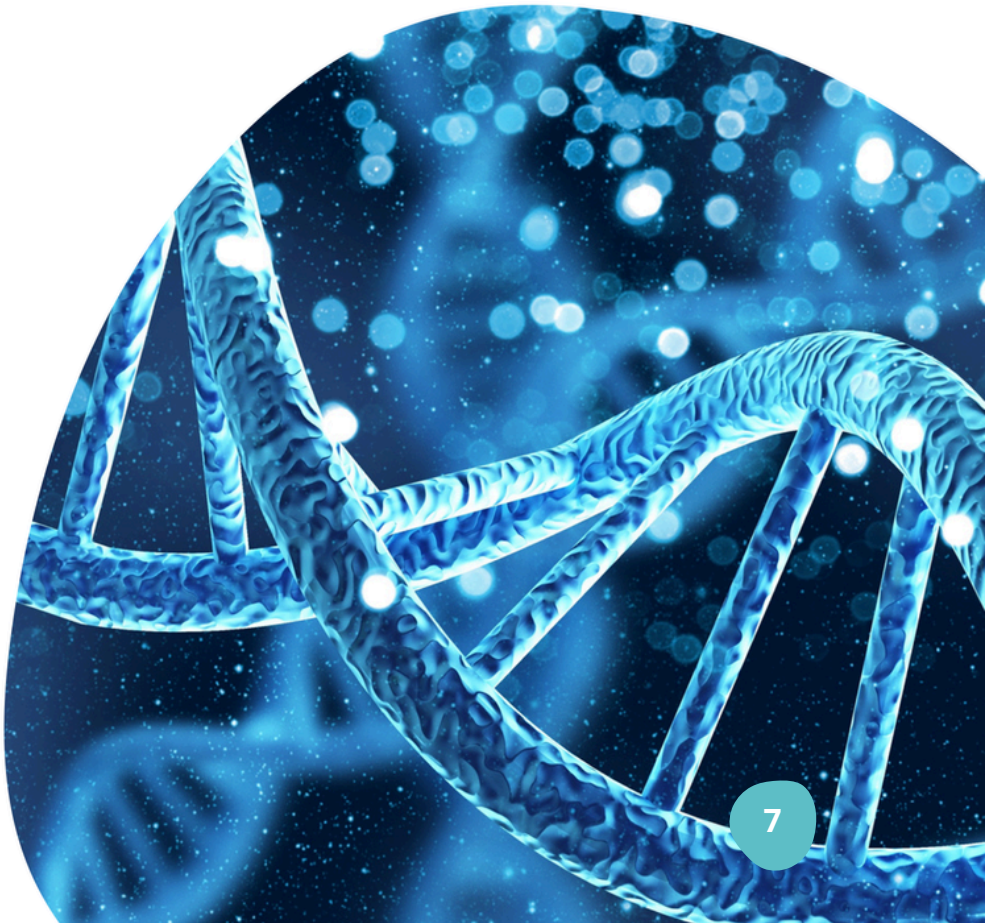
5-MTHF	5-Methyltetrahydrofolate
5,10-MTHF	5,10-Methylenetetrahydrofolate
DMG	Dimethylglycine
HVA	Homovanillic acid
SAH	S-adenosylhomocysteine
SAM	S-adenosylmethionine
THF	Tetrahydrofolate
VMA	Vanillylmandelic acid

Cofactors

BH4	Tetrahydrobiopterin
Fe	Iron
K	Potassium
Mg	Magnesium
SAM	S-adenosylmethionine
Zn	Zinc

Enzymes

AHCY	Adenosylhomocysteinase
BHMT	Betaine-homocysteine S-methyltransferase
CBS	Cystathionine beta-synthase
COMT	Catechol-O-methyltransferase
CTH	Cystathionine gamma-lyase
GNMT	Glycine N-methyltransferase
MAT	Methionine adenosyltransferase 1A
MT	Methyltransferases
MTHFR	Methylenetetrahydrofolate reductase
MTR	Methionine synthase
MTRR	Methionine synthase reductase
NOS	Nitric oxide synthase 3
SHMT	Serine hydroxymethyltransferase 1



Genetic Diversity

Research indicates that humans share 99.9% of their DNA, with the remaining 0.1% accounting for differences in physical traits (such as height, intelligence, hair, and eye color), disease risk, and reactions to drugs and nutrients.[31]

Genetic differences can be cataloged as various types of variations, including single nucleotide polymorphisms (SNPs).

Interpreting SNP results

A SNP (pronounced "snip") is a variation in a single nucleotide (A, T, C, or G) that occurs at a specific position (rsID) in the DNA sequence. SNPs can occur in coding regions (exons), non-coding regions (introns), or regulatory regions of genes. By studying SNPs, researchers can gain insights into genetic associations with various health conditions and traits, potentially leading to personalized medicine and targeted treatments.

SNPs can have multiple possible variants at a specific location, including the reference (wild type) allele and other alternative alleles (variant alleles). SNPs are categorized based on their relationship to a reference sequence.

Methylation Results Summary

The Methylation Results Summary displays the **gene name** (e.g., MTHFR) and the rsID (e.g., rs1801131) and indicates whether **genetic risk** is normal or elevated. If risk is elevated, it also reports potential impact.

Methylation			⊕⊕ Homozygous Variant	⊕⊖ Heterozygous	⊖⊖ Homozygous Wild
Test Name	Gene Name	Risk Association	Your Variant	Your Risk	Reference
rs1801133	MTHFR	Active folate deficiency	⊕⊖ C/T	Partially elevated	C/C
rs1801131	MTHFR	Active folate deficiency	⊕⊕ A/A	Normal	A/C, A/A

Methylation Complete Report

Methylation Complete Report

The Methylation Complete Report displays the **gene name** (e.g., MTHFR), the **rsID** (e.g., rs1801131), the **result** (e.g., A/C), and indicates whether **risk** is normal, elevated, or partially elevated.

Methylation			⊕⊕ Homozygous Variant	⊕⊖ Heterozygous	⊖⊖ Homozygous Wild
Test Name	Gene Name	Risk Association	Your Variant	Your Risk	Reference
rs10948059	GNMT	Methionine and SAMe build up in the blood	⊕⊕ T/T	Elevated	C/C

The glycine N-methyltransferase gene (GNMT) regulates the production of the enzyme glycine N-methyltransferase which is involved in the methylation of glycine and S-adenosylmethionine (SAMe) to N-dimethylglycine and S-adenosylhomocysteine (SAH) involved in cell growth and the regulation of gene expression. The mutation causes decreased expression of the gene and impairs the breakdown of methionine and SAMe, causing it to build up in the blood, abnormal methylation of DNA, cytotoxicity, and impaired DNA formation.Homozygous mutant (abnormal) individuals may have decreased gene expression and impaired methylation. Individuals with genetic susceptibility may benefit from consuming methylated folate supplements. Foods like kale, spinach, bok choy, escarole, collard greens, beet greens, mustard greens, turnip greens, arugula, broccoli, cabbage, Brussels sprouts, cauliflower, beetroot, beans, legumes, okra, mushroom, beef liver, the chicken liver can be included in the diet. Dietary supplements like magnesium and folate can also be beneficial.

You get one copy of each gene from each parent, so each gene has three possibilities:

- **Homozygous Wild:** Two copies of the normal "wild type" allele. Homozygous wild occurs most often and is typically considered the “normal” type with the least risk.
- **Homozygous Variant:** Two copies of a variant allele. This variant occurs least often and is usually associated with increased risk.
- **Heterozygous:** one copy of the normal "wild type" allele and one copy of the variant allele. Depending on the gene and rs location, a heterozygous variant may or may not result in elevated risk.

Test Name	Gene Name	Risk Association	Your Variant	Your Risk	Reference
rs1801133	MTHFR	Active folate deficiency	⊕⊖C/T	Partially elevated	C/C

For MTHFR, C is the normal (wild type) allele, and T is the variant allele.

The example above shows a heterozygous (C/T) result, meaning the patient has one copy of the normal "wild type" allele (C) and one copy of the variant allele (T). In this case, one copy of the variant allele results in elevated risk.

Table 1: Genotype Key

Genotype	Gene Name	SNP ID	Result	Genetic Risk
Homozygous Wild	MTHFR	rs1801133	C/C	Normal — —
Heterozygous	MTHFR	rs1801131	A/C	Elevated — +
Homozygous Variant	MAT1A	rs3851059	A/A	Elevated + +

Gene Function

MTHFR
The MTHFR gene encodes for the enzyme methylenetetrahydrofolate reductase, which is responsible for the conversion of 5, 10-methylenetetrahydrofolate, known as inactive folate (vitamin B9) to 5-methyltetra-hydrofolate (5-MTHF) also known as active folate. As active folate is necessary for converting homocysteine to methionine, MTHFR SNPs may contribute to elevated homocysteine levels. Individuals with the homozygous variant genotype are likelier to have reduced enzyme activity, leading to impaired folate metabolism.

COMT
The COMT gene encodes for the catechol-o-methyltransferase enzyme, which functions in the liver, kidney, and nerve cells and is critical in regulating neurotransmitter and hormone levels and detoxification.

MTR
The MTR gene codes for the enzyme methionine synthase, which converts homocysteine to methionine. It requires vitamin B12 and the enzyme methionine synthase reductase (regulated by the MTRR gene) to function properly.

MTRR
The MTRR gene codes for the enzyme methionine synthase reductase, which works with the enzyme methionine synthase (MTR) to reduce oxidized forms of vitamin B12 to be reused, converting homocysteine back to methionine.

MAT1A
MAT1A gene codes for the enzyme methionine adenosyltransferase 1A, which converts methionine to SAM.

SHMT1
SHMT1 gene codes for the enzyme serine hydroxymethyltransferase 1, which is responsible for the bidirectional conversion of serine and tetrahydrofolate to glycine and 5,10-methylenetetrahydrofolate, respectively.

GNMT
GNMT gene codes for the enzyme glycine-N-methyltransferase, which removes excess SAM when methionine and SAM are high. GNMT catalyzes the methyl group transfer from SAM to glycine, forming sarcosine. This process is downregulated in response to low methylfolate (active folate) and SAM levels.

BHMT
BHMT gene codes for the enzyme betaine-homocysteine S-methyltransferase, which catalyzes the transfer of a methyl group from betaine to dimethylglycine and remethylates homocysteine back to methionine. BHMT also plays a role in choline oxidation to form betaine, a “backup” or “salvage” pathway favored in folate deficiency.

NOS3
The NOS3 gene codes for the enzyme endothelial nitric oxide synthase (eNOS), which synthesizes nitric oxide from L-arginine in the vascular endothelium. Variants of this gene are involved in hypertension, hyperlipidemia, and heart disease.

SNP Clinical Implications and Nutrition & Supplement Management Options

Table 2: Methylation Panel Genes, Associated SNPs, rsIDs, Enzyme Function, and Genotypes

Gene	SNPs	Enzyme	Dietary	
MTHFR	**MTHFR 677-rs1801133**	• Homozygous variant, T/T (abnormal), genotype are more likely to have **REDUCED** enzyme activity leading to impaired folate metabolism. • Heterozygous C/T (partially abnormal) genotype may have normal or impaired folate metabolism. • Individuals with heterozygous (C/T) and homozygous (T/T) variant (abnormal) MTHFR 677 genotypes increase the risk for folate therapy failure against hyperhomocysteinemia.[8] • Association of MTHFR 677 variant with MTHFR 1298 variant may increase the risk of folate treatment failure.[6] • The association of MTHFR 677 heterozygous (C/T) or homozygous variant (T/T) genotype with cardiovascular disease is stronger in individuals who also have a homozygous variant SHMT1 (T/T) genotype.[9] • Both MTHFR 677 and 1298 SNPs increase the risk of elevated homocysteine levels and thus have been associated with cardiovascular disease, various cancers, neural tube defects, and Parkinson's disease.[10] [11] [12]	**Dietary** Foods high in folate include: • Legumes • Asparagus • Leafy greens • Beets • Brussels sprouts • Broccoli • Liver • Eggs **Supplementation** 5-methyltetrahydrofolate *Note: Avoid folic acid if possible; folic acid is synthetic and poorly converted to active folate in many. Research has shown that unmetabolized folic acid paired with low B12 status is associated with reduced cognitive performance.*	
	MTHFR 1298-rs1801131	• Homozygous variants, such as C/C (abnormal) genotypes, are more likely to have **REDUCED** enzyme activity, leading to impaired folate metabolism. • Heterozygous A/C (partially abnormal) genotype may have normal or impaired folate metabolism. • Both MTHFR 677 and 1298 SNPs increase the risk of elevated homocysteine levels and thus have been associated with cardiovascular disease, various cancers, neural tube defects, and Parkinson's disease.[2] [3] [4] • Association of MTHFR 677 variant with MTHFR 1298 variant may increase the risk of folate treatment failure.[14]		
MTRR	**rs1801394 rs162036**	• Homozygous variant G/G (abnormal) genotypes are likelier to have **REDUCED** enzyme function and possibly increased homocysteine levels. • Heterozygous A/G (partially abnormal) genotype may have **REDUCED** enzyme function and possibly increased homocysteine levels. • MTRR SNPs have been associated with elevated homocysteine levels and Down syndrome.[22]	**Dietary** Foods high in the MTRR cofactor vitamin B2 (riboflavin) include: • Spinach • Eggs • Liver • Almonds • Yogurt • Sundried tomatoes • Quinoa Foods high in the MTRR cofactor vitamin B3 (niacin) include: • Liver • Chicken breast • Tuna • Turkey • Avocado	Foods high in methionine to support the synthesis of the MTRR cofactor SAM include: • Wild-caught fish • Egg whites • Turkey • Seaweed • Oats • Brazil nuts • Beans **Supplementation** • Vitamin B2 (riboflavin) • Vitamin B3 (niacin) • Grass-fed whey protein powder, which is rich in methionine • L-methionine

Gene	SNPs	Enzyme	Dietary	
MAT1A	**rs3851059**	• Homozygous A/A (abnormal) genotypes are likelier to have **REDUCED** enzyme activity and decreased SAM production. • Heterozygous A/G (partially abnormal) genotype may have **REDUCED** enzyme activity and decreased SAM production. • The MAT1A SNP has been associated with increased stroke risk independent of homocysteine levels.[26]	**Dietary** Focus on adequate protein and fat at each meal to support the MAT1A cofactor ATP Foods high in the MAT1A cofactor potassium include: • Avocado • Lima beans • Swiss chard • Acorn squash	• Spinach • Sweet potato • Salmon Foods high in the MAT1A cofactor magnesium include: • Spinach • Almonds • Pumpkin seeds • Black beans • Dark chocolate • Sunflower seeds • Flaxseeds
SHMT1	**rs1979277**	• Homozygous T/T (abnormal) genotypes are likelier to have REDUCED enzyme activity and decreased 5-methyltetrahydrofolate (5-MTHF) levels. • Heterozygous C/T (partially abnormal) genotype may have REDUCED enzyme activity and decreased 5-methyltetrahydrofolate (5-MTHF) levels. • The SHMT1 SNP may be associated with fetal growth restriction of fetuses of women who have this SNP.[24] • The association of *MTHFR 677* rs1801133 heterozygous (C/T) or homozygous variant (T/T) genotype with cardiovascular disease is stronger in individuals who also have a homozygous variant SHMT1 (T/T) genotype.[8]	**Dietary** Foods high in the SHMT1 cofactor iron include: • Spinach • Liver • Eggs • Dark chocolate • Lentils • Black beans • Sardines • Pumpkin seeds • Tofu	Foods high in the SHMT1 cofactor vitamin B6 (pyridoxine) include: • Salmon • Turkey • Eggs • Pistachios • Pinto beans • Avocado • Chickpeas • Sunflower and sesame seeds
GNMT	**rs10948059**	• Homozygous T/T (abnormal) genotypes are more likely to have **INCREASED** enzyme function, leading to an increase in **homocysteine, particularly in the setting of an MTHFR SNP.** • Heterozygous C/T (partially abnormal) genotype may have **INCREASED** enzyme function, leading to a possible increase in **homocysteine.** • Although the GNMT SNP has been associated with a possible increase in homocysteine as a backup pathway to convert SAM to SAH, it has also been linked to the benefit of upregulation of antioxidant and detoxification genes.[27]	**Dietary** Foods high in the GNMT substrate glycine include: • Animal proteins • Seafood • Soybeans • Seaweed • Eggs • Amaranth • Peanuts • Almond	• Seeds (pumpkin, sunflower) • Lentils **Supplementation** • Glycine powder • Magnesium Glycinate
BHMT	**rs3733890**	• Homozygous A/A (abnormal) genotypes are more likely to have **INCREASED** enzyme activity and hyperhomocysteinemia. • Heterozygous A/G (partially abnormal) genotype may have **INCREASED** enzyme activity and possible hyperhomocysteinemia. • The BHMT SNP may be beneficial as a backup pathway to recycle homocysteine to methionine. Still, there remains scientific uncertainty as this SNP may lead to the loss of function of the BHMT enzyme, especially in the setting of poor folate-dependent remethylation of homocysteine. The result is thought to be increased homocysteine levels due to mutation of zinc-binding domains. • It has also been theorized that in times of elevated homocysteine, liver betaine stores may become depleted due to this SNP's upregulating impact on enzyme function, which uses betaine as a substrate.[28]	**Dietary** Foods high in the BHMT substrate choline include: • Lentils • Soybeans • Mushrooms • Egg yolks • Liver • Beef • Salmon Foods high in the BHMT substrate betaine include: • Beets • Quinoa • Broccoli • Spinach • Sunflower seeds	Foods high in the BHMT cofactor zinc include: • Oysters • Grass-fed beef • Liver • Lamb • Hemp seeds • Pumpkin seeds • Cashews • Lentils **Supplementation** • Zinc • Trimethylglycine (TMG), a.k.a. betaine • Choline or citicoline *Consider testing zinc and choline status with the Vibrant Micronutrient Test.*

Gene	SNPs	Enzyme	Dietary	
MTR	**rs1805087**	• Individuals with homozygous variant G/G (abnormal) genotype are more likely to have **INCREASED** MTR enzyme activity. • Individuals with heterozygous A/G (partially abnormal) genotype may have **INCREASED** MTR enzyme activity. • Although the MTR SNP has a beneficial impact on methylation overall in that it upregulates the recycling of homocysteine to methionine, this SNP has been associated with congenital heart disease, Down syndrome, dementia, and depression.[23] [24] This SNP may also be related to fetal growth restriction of fetuses of women who have this SNP.[25]	**Dietary** Foods high in the MTR substrate vitamin B12 include: • Shellfish • Sardines • Liver • Nutritional yeast and other fortified foods and beverages Foods high in the MTR substrate folate include: • Legumes • Asparagus • Leafy greens • Beets • Brussels sprouts	• Broccoli • Eggs • Liver Foods high in the MTR cofactor zinc include: • Oysters • Grass-fed beef • Liver • Lamb • Hemp seeds • Pumpkin seeds • Cashews • Lentils **Supplementation** • Vitamin B12 • Folate • Zinc
COMT	**rs4680**	• Homozygous variant, A/A (abnormal), genotype is more likely to have **REDUCED** COMT enzymatic activity, which increases dopamine levels in the brain. • Heterozygous (partially abnormal) genotypes have intermediate brain dopamine levels, which may affect their neural performance. • COMT SNPs have been associated with mood and anxiety disorders, including bipolar disorder and anxiety disorder, eating disorders, migraine, and fibromyalgia.[15] [16] [17] [18] • These individuals are more vulnerable to stress but have good memory and attention to tasks. This is the "Worrier" genotype.[19]	**Dietary** Foods high in the COMT cofactor magnesium include: • Spinach • Almonds • Pumpkin seeds • Black beans • Dark chocolate • Sunflower seeds • Flax seeds	Foods high in methionine to support the synthesis of the COMT cofactor SAM include: • Wild-caught fish • Egg whites • Turkey • Seaweed • Oats • Brazil nuts **Supplementation** • Magnesium • SAMe • L-methionine
	rs4633	• Individuals with homozygous T/T (abnormal) genotype are likelier to have impaired COMT enzyme activity and impaired catecholamine and estrogen conversion. • Individuals with heterozygous, C/T (partially abnormal) genotype may have impaired COMT enzyme activity and impaired catecholamine and estrogen conversion. • As the COMT enzyme is necessary for the detoxification of estrogens to less active metabolites, SNPs may lead to oxidative DNA damage via more DNA-reactive unprocessed estrogens (4-OH forms) and, therefore, are thought to be associated with an increased risk of hormone-dependent cancers such as breast and endometrial cancer, **although results remain inconclusive.**[20] [21] [22]		
NOS3	**rs1799983**	• Homozygous T/T (abnormal) genotypes are likelier to have **REDUCED** eNOS enzyme activity and impaired nitric oxide release. • Heterozygous G/T (partially abnormal) genotype may have **REDUCED** eNOS enzyme activity and impaired nitric oxide release. • The NOS3 polymorphism slows nitric oxide synthesis, increasing the risk of endothelial dysfunction and cardiovascular diseases such as hypertension and coronary artery disease.[29] [30]	**Dietary** • Foods high in the NOS3 substrate arginine include: • Pumpkin seeds • Sunflower seeds • Brazil nuts • Fish • Eggs • Walnuts • Beef • Coconut meat	**Supplementation** • L-arginine* • Protein powder (grass-fed whey or collagen or pea protein) • Consider testing arginine levels on Micronutrient 3.0 test and replete as necessary. **Caution: Taking blood pressure lowering medications may potentiate the effect.*

Disclaimer and Regulatory Statement

This Methylation Panel Interpretive Guide is intended to be used in tandem with Vibrant Wellness's Methylation Panel Test, and this guide is provided to users pursuant to the Terms of Use Agreement (the "Terms") on its website www.vibrant-wellness.com.

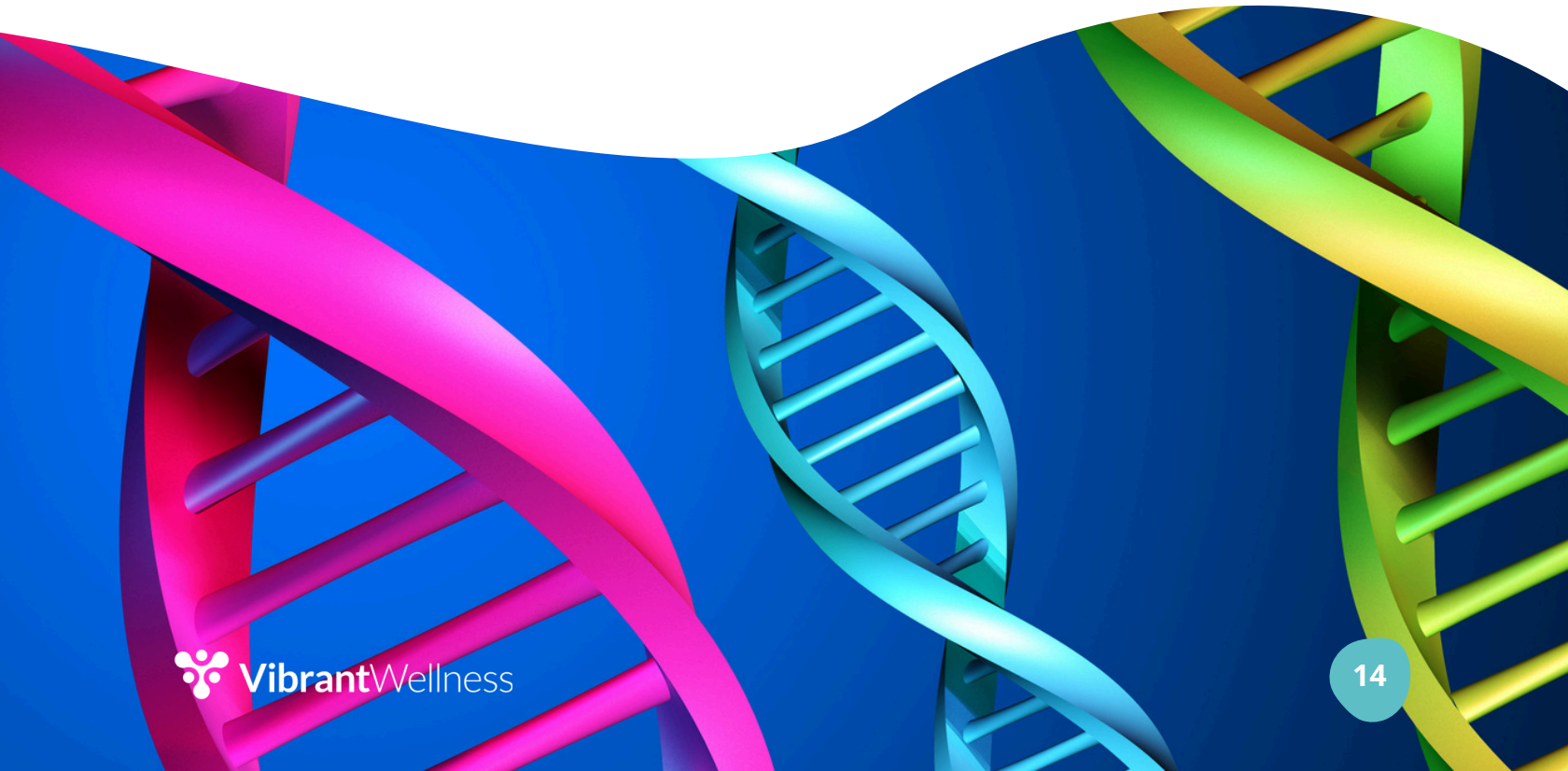
The content within this interpretive guide is not intended to be a stand-alone medical reference guide, nor is it intended to be a substitute for medical advice from a healthcare provider. The wellness test and interpretive guide is intended to encourage a general state of health and well-being for adults while referring to diseases or conditions. This guide is not intended for children, pregnant or lactating, or immunocompromised persons, and is not meant to diagnose, treat, or cure any disease or condition.

The clients who receive Vibrant Wellness Methylation Panel test results are advised to consult their physician and/or health care provider team for diagnosis and further follow up care, including but not limited to additional testing, prescription medication, and any treatment interventions including diet, exercise, or lifestyle management.

The Vibrant Wellness platform provides tools to track and analyze general wellness profiles and encourage a general state of health and well-being. Vibrant testing does not demonstrate absolute positive and negative predictive values for any disease state or condition. Its clinical utility has not been fully established.

Vibrant validates the accuracy and precision of the testing but not of its clinical or diagnostic value. So, these tests are for wellness and informational purposes only. Vibrant is actively doing clinical research on these samples, de-identified from patients under an IRB and will make research publications towards the same as and when the clinical utility is well established.

These tests have been laboratory developed and their performance characteristics determined by Vibrant America LLC, a CLIA-certified laboratory performing the test CLIA#:05D2078809. The test has not been cleared or approved by the U.S. Food and Drug Administration (FDA). Although FDA does not currently clear or approve laboratory-developed tests in the U.S., certification of the laboratory is required under CLIA to ensure the quality and validity of the tests.



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