

UPCOMING EVENTS

**Harnessing the Microbiome
to Boost GLP-1: Insights
from the GI360™**

Presented by Jeannie Gorman, MS, CCN
May 6, 2026 at 12 PM Pacific

**Saliva, Urine, or Blood?
Choosing the Right Hormone
Test for Your Patients**

Presented by Dr. Brandon Lundell, DC
May 13, 2026 at 12 PM Pacific

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**Wellness
Wednesday**

WILL BEGIN SHORTLY

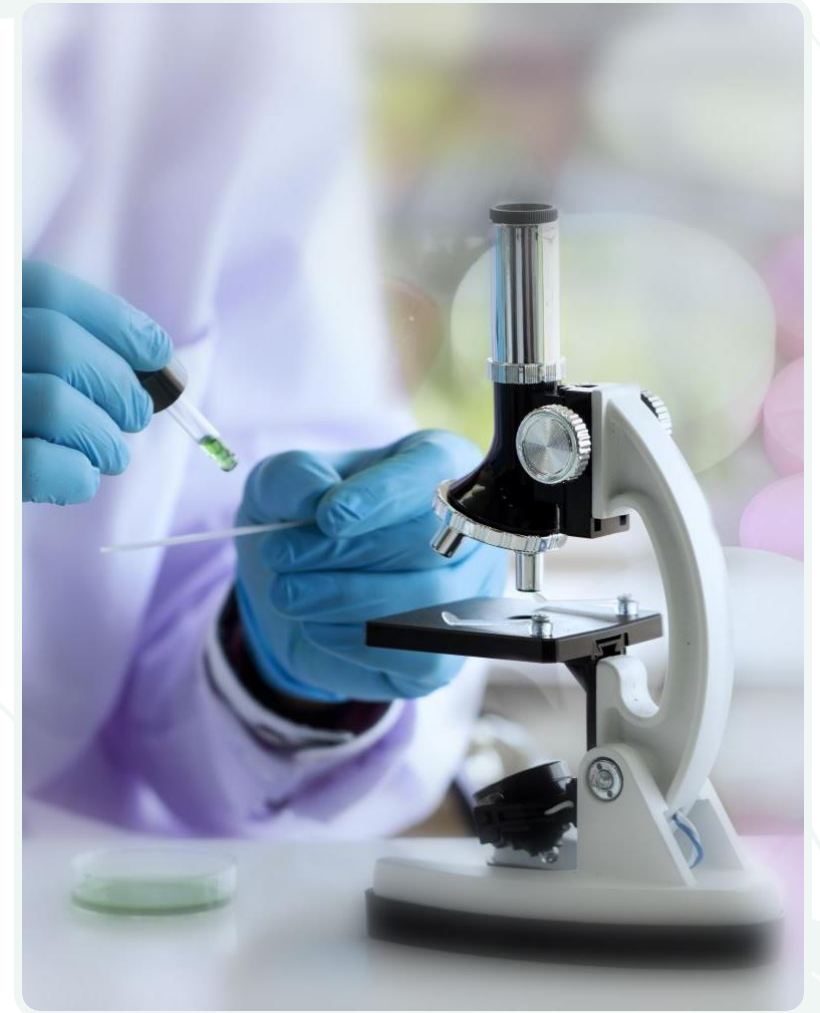
Methylation and Clinical Practice: Insights from the Doctor's Data Methylation Profile

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Learning Objectives

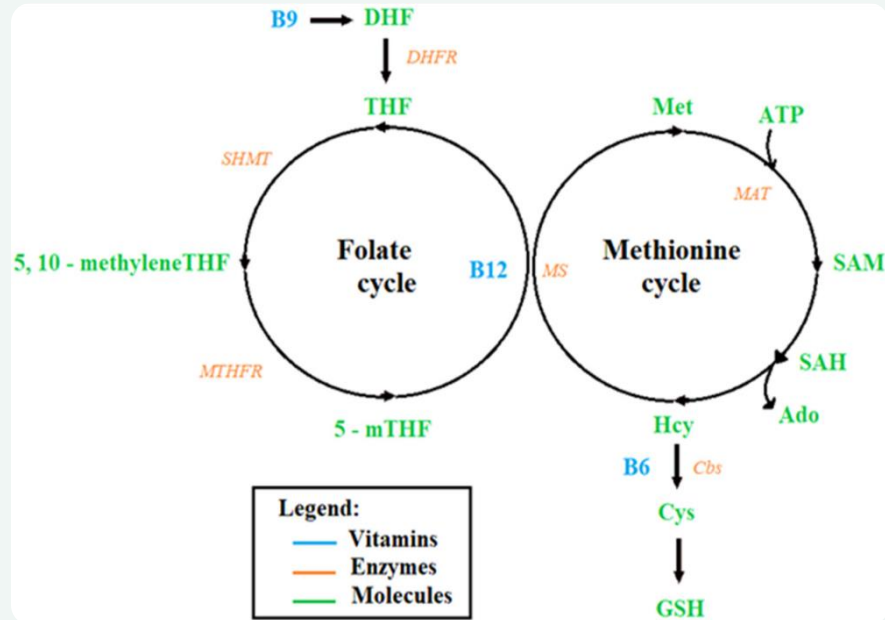
- 🌱 Understand the role of methylation in human physiology
- 🌱 Explore the clinical significance of methylation imbalances
- 🌱 Review the components and interpretation of the Doctor's Data Methylation Profile
- 🌱 Discuss case applications and therapeutic strategies based on methylation status



Methylation:

The biochemical process of adding a *methyl group* ($-CH_3$) to a molecule, typically DNA, proteins, or other compounds

- 🌱 **Gene regulation:** DNA methylation can silence or activate genes without altering the DNA sequence
 - 🌱 Governing epigenetics
- 🌱 **Detoxification:** Methylation helps process and eliminate toxins, hormones, and heavy metals
- 🌱 **Neurotransmitter synthesis:** It supports the production and breakdown of dopamine, serotonin, etc.
- 🌱 **Cellular repair and replication:** Methylation is essential for DNA repair & RNA repair and cell division
 - 🌱 Plays a direct role in cellular membrane phospholipid metabolism
- 🌱 **Homocysteine metabolism:** It converts homocysteine into methionine, impacting cardiovascular and neurological health



Folate & Methionine Cycles: Methylation Metabolism

Roufael M, Bitar T, Sacre Y, Andres C, Hleihel W. Folate–Methionine Cycle Disruptions in ASD Patients and Possible Interventions: A Systematic Review. *Genes*. 2023; 14(3):709. <https://doi.org/10.3390/genes14030709>

Clinical Implications of Methylation Imbalances

Cardiovascular
diseases

Neuropsychiatric
disorders

Detoxification

Reproductive &
Hormone Health

Autoimmune &
Cancer

Assessing Methylation Status



Functional Testing

Functional assays measuring metabolite levels



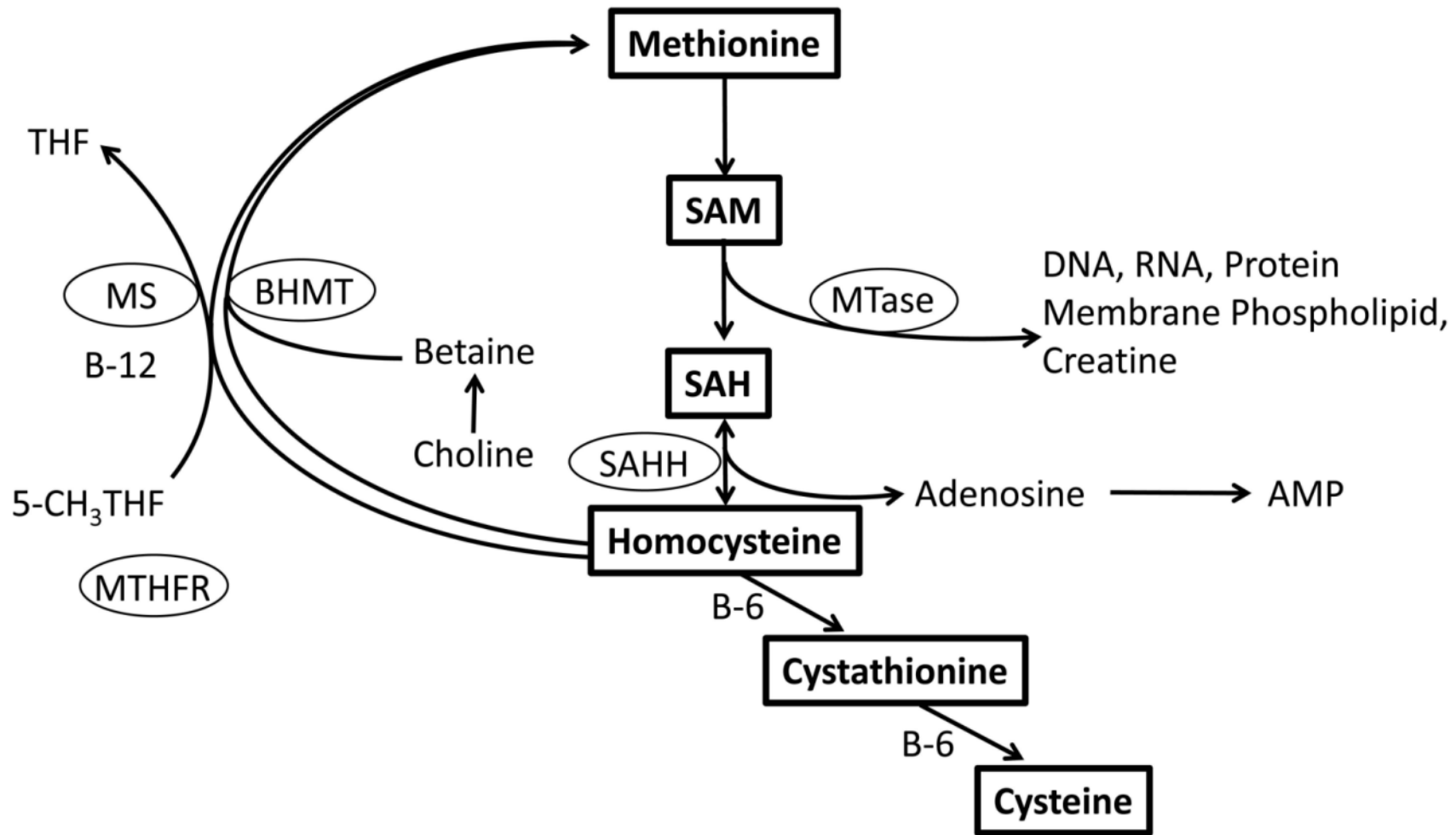
Genetic Testing

Genetic testing for SNPs (e.g., MTHFR mutations)

Functional assessment of methylation

- 🌱 Sample type: Plasma
- 🌱 Analytical method: Liquid chromatography (LCP-MS)
- 🌱 Analytes: methionine, SAMe, SAH, homocysteine, cystathionine, cysteine
- 🌱 SAM:SAH ratio







Methylation Biomarkers

- 🌱 Methionine
- 🌱 S-adenosylmethionine (SAM)
- 🌱 S-adenosylhomocysteine (SAH)
- 🌱 Homocysteine
- 🌱 Cystathionine
- 🌱 Cysteine
- 🌱 Methylation Index (SAM/SAH ratio)

Methionine (Met)

- 🌱 An essential amino acid
- 🌱 High in animal proteins: eggs, fish, poultry, beef
- 🌱 Moderate in nuts, seeds, and legumes
- 🌱 The starting amino acid in nearly all protein synthesis (coded by the AUG start codon)
- 🌱 The precursor to S-adenosylmethionine (SAME), the body's universal methyl donor
- 🌱 Too little: Impaired methylation, low glutathione, poor detox
- 🌱 Too much (especially with poor methylation): Elevated homocysteine, oxidative stress

S-adenosylmethionine(SAM/SAMe)

- Methylation, neurotransmitter synthesis, and detoxification
- It's synthesized in the body from methionine and ATP via the enzyme methionine adenosyltransferase
- Primary methyl donor
 - Epigenetic regulation: DNA and histones
 - Neurotransmitters
 - Membrane phospholipids
 - Detoxification Pathways
- Associated with enhanced monoamine synthesis and depression
- Caution with supplementation
 - Can trigger mania in bipolar disorder
 - Potential interactions with MAOIs, SSRIs and serotonergic agents
 - Can potentially worsen anxiety in individuals with certain *COMT* and *MAOA*

S-adenosylhomocysteine (SAH)

- Formed when SAdMe donates a methyl group to a substrate
- A potent inhibitor of methyltransferase enzyme
 - Slows or blocks methylation reactions
 - Level influencing gene expression, neurotransmitter balance, etc.
- Reversibly hydrolyzed into homocysteine and adenosine by the enzyme SAH hydrolase
 - Favors SAH formation
 - Efficient clearance of homocysteine is critical (B12)
- Elevated SAH is associated with cardiovascular disease, neurodegeneration, and epigenetic dysregulation

Homocysteine (HCys)

- 🌱 An essential, sulfur-containing, amino acid
- 🌱 Clinical marker for cardiovascular, neurological, and methylation-related dysfunction
- 🌱 SAH is then hydrolyzed into homocysteine and adenosine
- 🌱 Hyperhomocysteinemia: biomarker for cardiovascular, neurological, and methylation-related dysfunction
- 🌱 Remethylation back to methionine via primary route (MTR, MTRR, MTHFR) and secondary route (BHMT & TMG)
- 🌱 Transsulfuration to cystathionine → cysteine → glutathione (B6/P5P)

Cystathionine (Cth)

- 🌱 Formed via the enzyme *cystathionine β -synthase* (CBS), via the reaction between homocysteine and serine
 - 🌱 Depends on vitamin B6 (P5P) and Fe
- 🌱 A key intermediate in the transsulfuration pathway
- 🌱 Plays a central role in sulfur amino acid metabolism and is crucial for maintaining redox balance and methylation efficiency
- 🌱 Can indicate methylation-transsulfuration balance, GSH production (via cysteine), B6 status
- 🌱 Converted into cysteine by *cystathionine γ -lyase* (CTH)
 - 🌱 Leads to GSH production

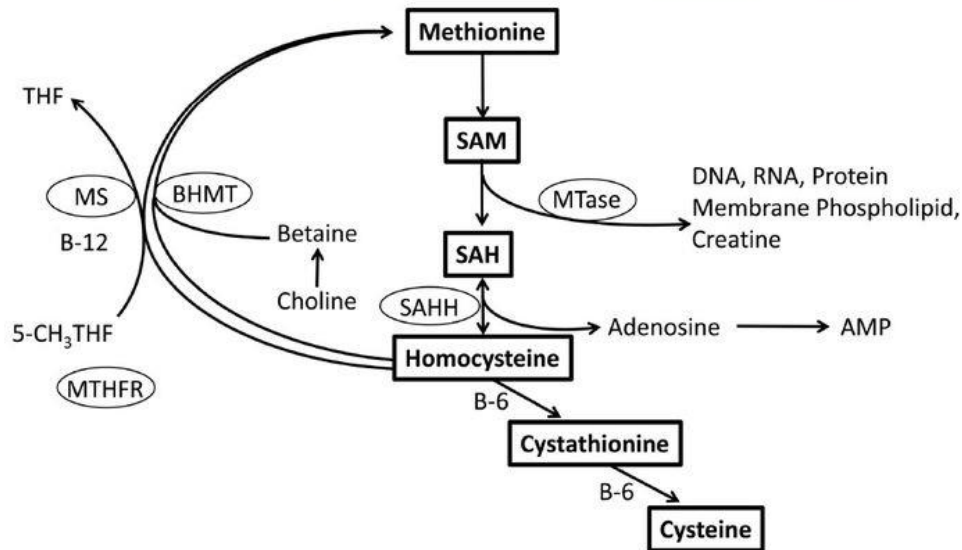
Cysteine (Cys)

- 🌱 A *semi-essential* sulfur-containing amino acid
 - 🌱 Can be synthesized from methionine, but under stress or illness, dietary intake becomes more important
- 🌱 The rate-limiting precursor for glutathione (GSH)
- 🌱 Its thiol (-SH) group allows cysteine residues in proteins to form disulfide bridges, stabilizing protein structure
 - 🌱 Especially in keratin, ie. hair, skin, nails
- 🌱 Via GSH and other sulfur pathways, cysteine helps neutralize heavy metals, xenobiotics, and reactive oxygen species
- 🌱 Influences redox-sensitive transcription factors like Nrf2, which regulate antioxidant and detox genes

Methylation Profile; plasma

PRIMARY & INTERMEDIATE METABOLITES							
	RESULT/UNIT	REFERENCE INTERVAL	PERCENTILE				
			2.5 th	16 th	50 th	84 th	97.5 th
Methionine	3.4 $\mu\text{mol/dL}$	1.6 - 3.6					
Cysteine	22 $\mu\text{mol/dL}$	20 - 38					
S-adenosylmethionine (SAM)	97 nmol/L	86 - 145					
S-adenosylhomocysteine (SAH)	19.4 nmol/L	10 - 22					
Homocysteine	4.2 $\mu\text{mol/L}$	< 11			68 th	95 th	
Cystathionine	0.01 $\mu\text{mol/dL}$	< 0.05					

METHYLATION INDEX				
	RESULT	REFERENCE INTERVAL	PERCENTILE	
			68 th	95 th
SAM : SAH	5.0	> 4		



Functional Assessment of Methylation

Methylation Index (SAM:SAH ratio)

- 🌱 **S-adenosylmethionine (SAM)**, the universal methyl donor used in DNA, RNA, neurotransmitter, and phospholipid methylation
- 🌱 **S-adenosylhomocysteine (SAH)**, the byproduct of methylation reactions, which *inhibits* methyltransferases if it accumulates
- 🌱 Divide the concentration of SAM by SAH
 - 🌱 Referred to as the methylation index
 - 🌱 A functional biomarker of methylation
- 🌱 Low methylation index is associated with global DNA hypomethylation, oxidative stress, and increased cardiovascular risk
 - 🌱 Plasma homocysteine
 - 🌱 SNPs (MTHFR, MTR, MTRR, BHMT, CBS)
- 🌱 A higher SAM/SAH ratio reflects a strong methylation potential
 - 🌱 SAM:SAH > 4
 - 🌱 An adequate balance of methyl donors (SAM) relative to inhibitors (SAH)
 - 🌱 Generally, indicates methylation reactions are proceeding efficiently, supporting processes ie. DNA repair, neurotransmitter synthesis, phospholipid metabolism, etc.

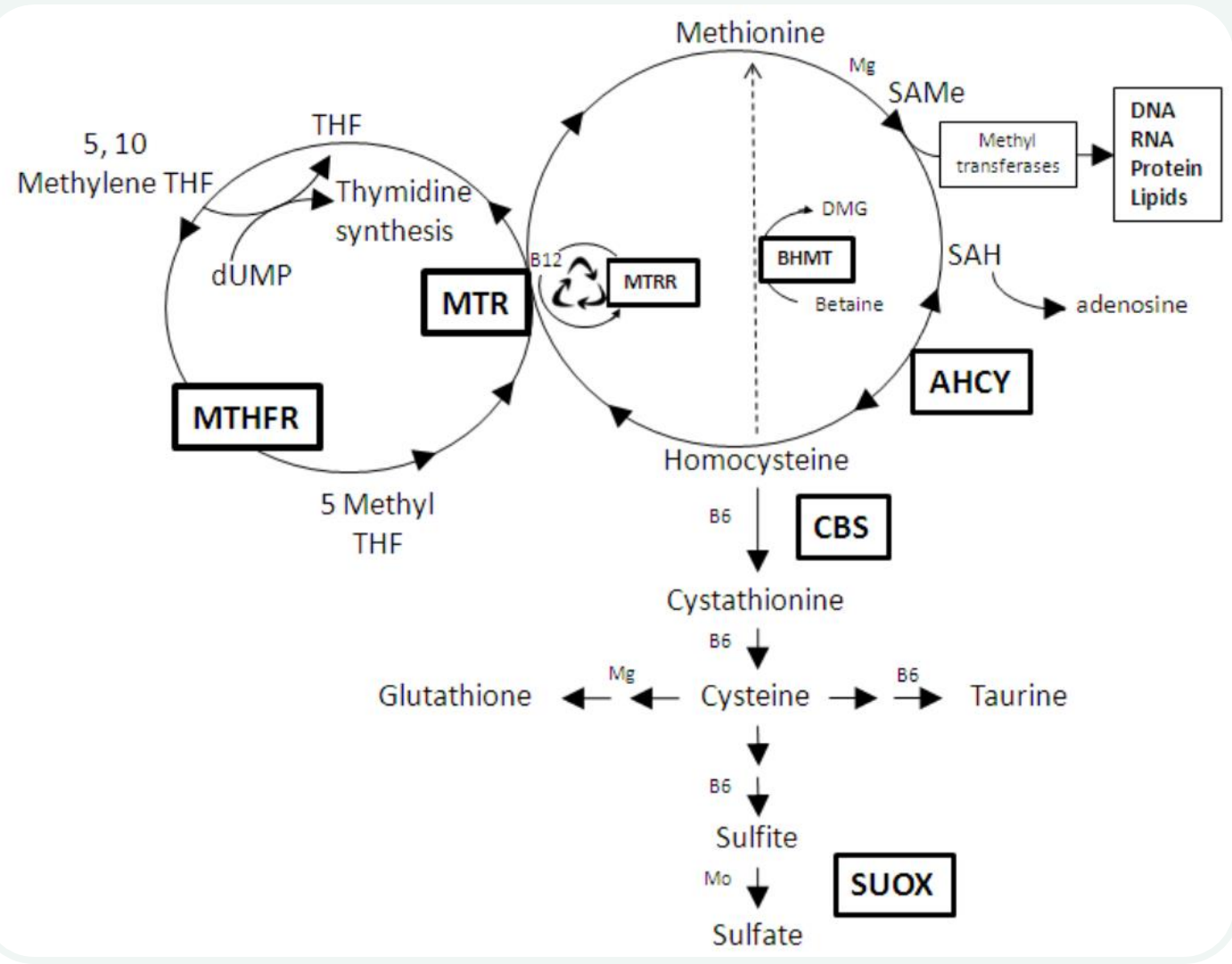
Low Methylation Index

Methylation Profile; plasma

PRIMARY & INTERMEDIATE METABOLITES						
	RESULT/UNIT	REFERENCE INTERVAL	PERCENTILE			
			2.5 th	16 th	50 th	84 th 97.5 th
Methionine	3.0 $\mu\text{mol/dL}$	1.6 - 3.6	[Bar chart showing result at 50th percentile]			
Cysteine	32 $\mu\text{mol/dL}$	20 - 38	[Bar chart showing result at 50th percentile]			
S-adenosylmethionine (SAM)	62 nmol/L	86 - 145	[Bar chart showing result at 68th percentile]			
S-adenosylhomocysteine (SAH)	35.1 nmol/L	10 - 22	[Bar chart showing result at 95th percentile]			
			68 th		95 th	
Homocysteine	9.5 $\mu\text{mol/L}$	< 11	[Bar chart showing result at 50th percentile]			
Cystathionine	0.02 $\mu\text{mol/dL}$	< 0.05	[Bar chart showing result at 50th percentile]			
METHYLATION INDEX						
	RESULT	REFERENCE INTERVAL	PERCENTILE			
			68 th		95 th	
SAM : SAH	1.8	> 4	[Bar chart showing result at 68th percentile]			

Low Methylation Index

- Low availability of methyl groups to hundreds of important molecules
 - DNA, RNA, proteins, choline, membrane phosphatidylcholine, creatine (liver), neurotransmitters and neurotransmitter receptors
- Diverse potential consequences of compromised methylation
 - Aberrant neurotransmitter metabolism, abnormal gene expression and silencing, cancer, cardiovascular disease and vascular occlusion, congenital heart disease/birth defects, neurodegenerative disease, autoimmune disease, and poor response to environmental toxins (e.g. endogenous detoxification of arsenic)
- Accumulation of SAH inhibits methyltransferase enzymes by product inhibition: SAH binds with high affinity to the active sites of MTs



Cases



Case 1

Patient: 50 yof

Presenting Concerns: Mild hypertension, fatigue, occasional tingling in her hands and feet

Medical History:

- 🌿 Family history of cardiovascular disease and early-onset Alzheimer's
- 🌿 History of anxiety and difficulty concentrating over the past 18 months
- 🌿 Vegetarian for 12 years
- 🌿 Periodic use of methylated B-complex supplements, though inconsistently
- 🌿 No alcohol, but moderate caffeine intake
- 🌿 Reports increased stress due to workload and caring for elderly parent

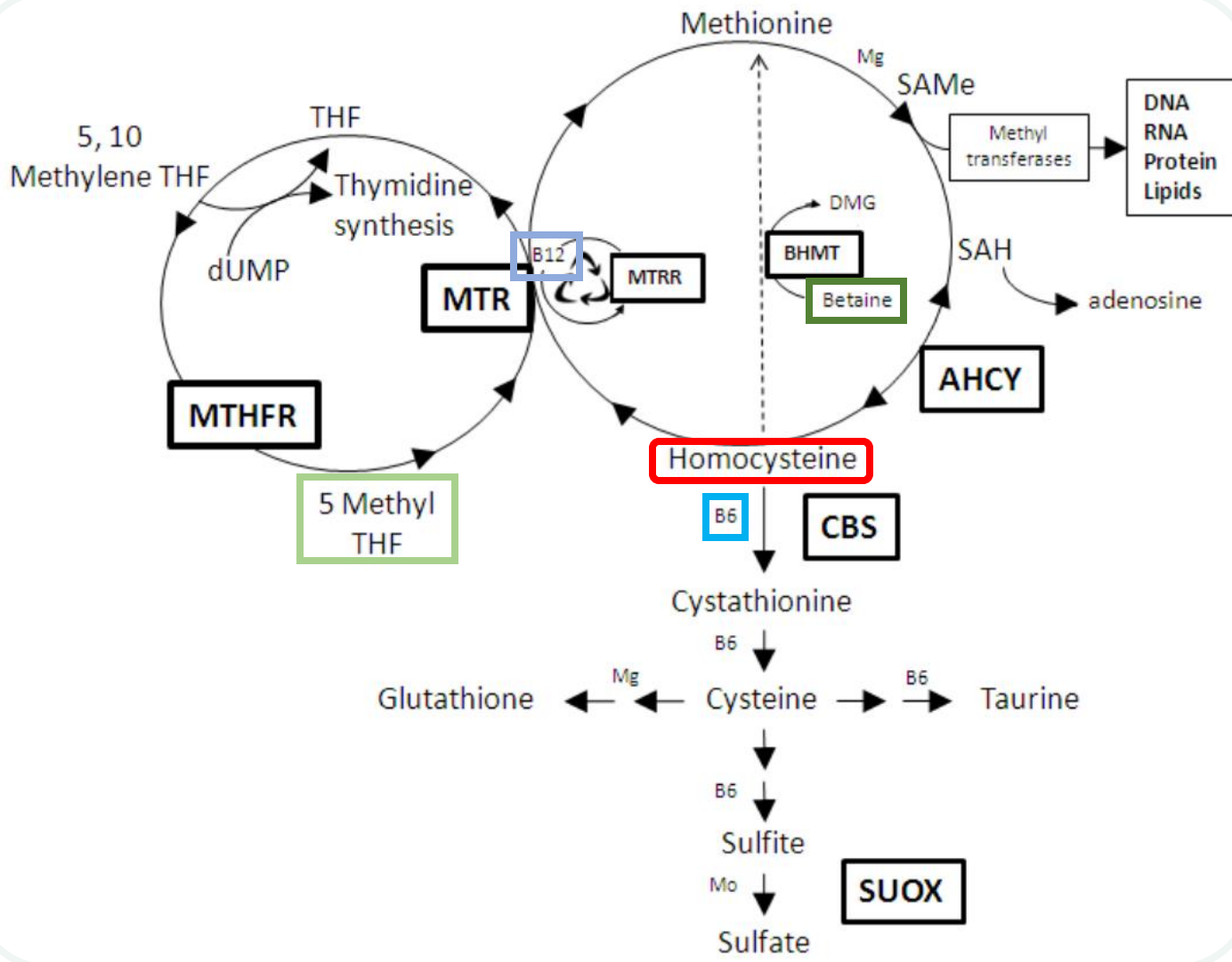
50 yof

Methylation Profile; plasma

PRIMARY & INTERMEDIATE METABOLITES									
	RESULT/UNIT		REFERENCE INTERVAL		PERCENTILE				
					2.5 th	16 th	50 th	84 th	97.5 th
Methionine	1.8	µmol/dL	1.6 -	3.6					
Cysteine	25	µmol/dL	20 -	38					
S-adenosylmethionine (SAM)	97	nmol/L	86 -	145					
S-adenosylhomocysteine (SAH)	17.6	nmol/L	10 -	22					
						68 th		95 th	
Homocysteine	12.7	µmol/L	<	11					
Cystathionine	0.01	µmol/dL	<	0.05					
METHYLATION INDEX									
	RESULT		REFERENCE INTERVAL		PERCENTILE				
					68 th	95 th			
SAM : SAH	5.5		>	4					

Case 1 Findings

- 🌱 Elevated Homocysteine: 12.7 $\mu\text{mol/L}$ (\uparrow elevated)
 - 🌱 B12 (lower d/t vegetarian diet, age, decreased stomach pH)
 - 🌱 Fatigue
 - 🌱 Tingling in extremities occasionally
 - 🌱 Vitamin B12, B6 (P5P) and B9 (folate)
 - 🌱 Family history of cardiovascular disease
 - 🌱 Continually monitor Hcys
 - 🌱 Comprehensive Cardiovascular Panel
- 🌱 Consider testing for MTRR, MTR, MTHFR
 - 🌱 Consider supplementing these enzymes
- 🌱 Consider testing for endothelial SNPs
 - 🌱 NOS/D298E
 - 🌱 Polymorphism in the NOS3 gene
 - 🌱 Encodes endothelial nitric oxide synthase (eNOS)



Decreasing Homocysteine

- 🌿 Methylfolate/5-MTHF
 - 🌿 400 mcg
- 🌿 Methylcobalamin/B12
 - 🌿 500 mcg
- 🌿 Pyridoxal-5-phosphate (P5P/B6)
 - 🌿 20 mg
- 🌿 Trimethylglycine (TMG/Betaine)
 - 🌿 500 mg
- 🌿 **Recheck:** 8–12 weeks
 - 🌿 Adjust based on response and tolerance

Case 2

Patient: 59 yom

Presenting Complaints: Brain fog, low energy, and recent increases in blood pressure (averaging 132/86 mmHg)

Medical History:

- 🌿 Father had a myocardial infarction at 57 yoa
- 🌿 Maternal history of type 2 diabetes
- 🌿 Professionally active with a high-stress managerial role
- 🌿 Struggles with sleep
- 🌿 Often skips meals during the day

59 yom

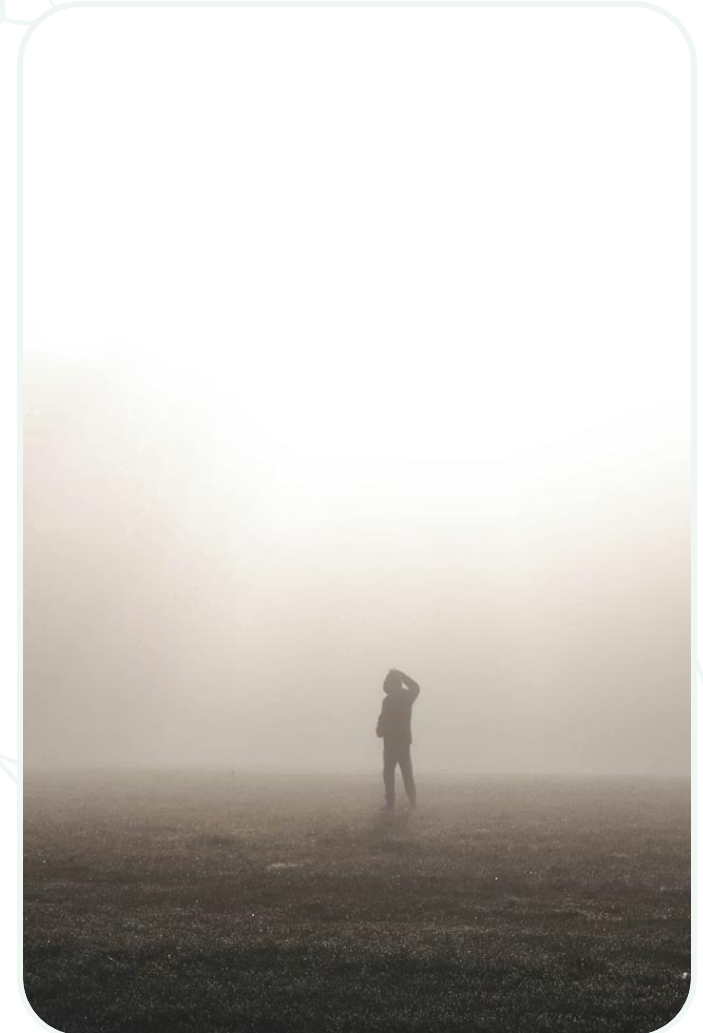
Methylation Profile; plasma

PRIMARY & INTERMEDIATE METABOLITES							
	RESULT/UNIT	REFERENCE INTERVAL	PERCENTILE				
			2.5 th	16 th	50 th	84 th	97.5 th
Methionine	2.5 $\mu\text{mol/dL}$	1.6 - 3.6					
Cysteine	27 $\mu\text{mol/dL}$	20 - 38					
S-adenosylmethionine (SAM)	75 nmol/L	86 - 145					
S-adenosylhomocysteine (SAH)	26.6 nmol/L	10 - 22					
				68 th		95 th	
Homocysteine	7.0 $\mu\text{mol/L}$	< 11					
Cystathionine	0.02 $\mu\text{mol/dL}$	< 0.05					
METHYLATION INDEX							
	RESULT	REFERENCE INTERVAL	PERCENTILE				
				68 th		95 th	
SAM : SAH	2.8	> 4					

Case 2 Findings

- 🌱 **SAM:** Low (75 nmol/L; 2.5th percentile)
 - 🌱 Brain fog, low energy
 - 🌱 Low methyl donor availability
- 🌱 **SAH:** High-normal (26.6 nmol/L; 84th percentile)
- 🌱 **SAM:** SAH Ratio: Low Methylation Index at 2.8 (goal >4.0)
 - 🌱 Reduced remethylation capacity
- 🌱 Homocysteine WNL
- 🌱 Prioritize stress management (HRV training, breathing exercises)

- 🌱 Consider genetic variants MAT, AHCY
- 🌱 Reassess labs in 8–12 weeks after protocol initiation



Addressing low Methylation Index

- 🌿 Phosphatidylcholine to increase bioavailability of SAM
 - 🌿 500 - 1,200 MG QD
- 🌿 Increase Methionine
 - 🌿 Dietary meat (turkey, tuna, beef (B12 (low energy))) and consistent meal intake
 - 🌿 200 to 500 mg QD
- 🌿 Support methionine adenosyltransferase (MAT) enzyme via Mg2+
 - 🌿 L-Threonate: Crosses the BBB
 - 🌿 1,000–2,000 mg QD (provides ~144–200 mg elemental magnesium)
 - 🌿 Taurate: Supports both nervous system and cardiovascular tone
 - 🌿 125–500 mg QD

Addressing low Methylation Index

🌿 Cobalamin

- 🌿 Supports decreasing SAH, energy
 - 🌿 Brain fog, low energy
- 🌿 Dietary B12 (from meat, dairy, etc)
- 🌿 500 mcg QD
- 🌿 Methylcobalamin
 - 🌿 Supports neurological and methylation pathways
- 🌿 Adenosylcobalamin
 - 🌿 Active form in the mitochondria (energy)
 - 🌿 Acts as a cofactor for methylmalonyl-CoA mutase

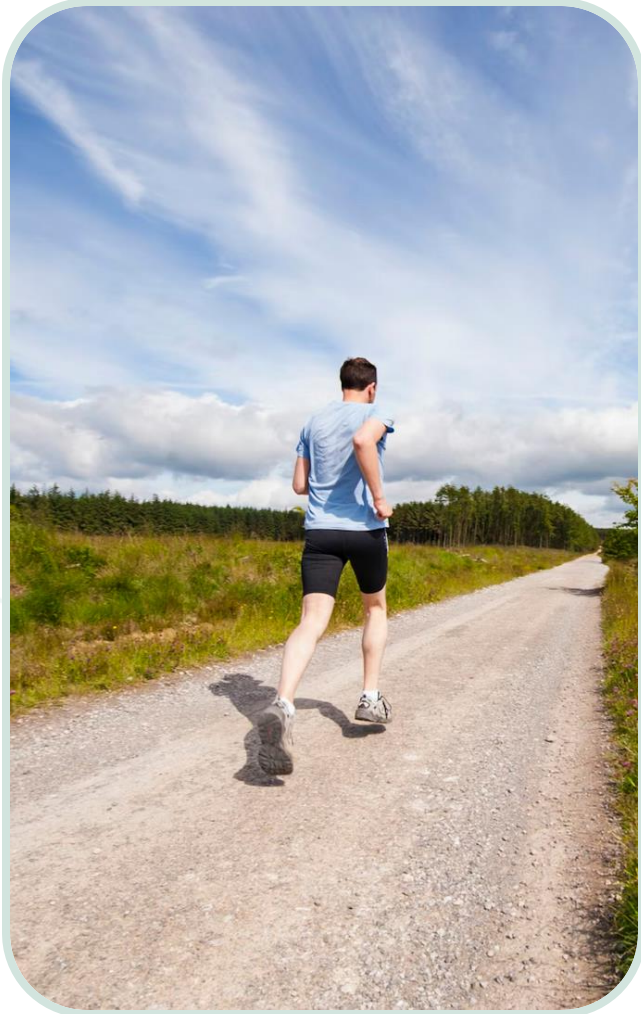
- 🌿 Supports mitochondrial function and fatty acid metabolism

🌿 Hydroxocobalamin

- 🌿 Produced by gut bacteria
- 🌿 Converts to methyl- and adenosylcobalamin

🌿 Cyanocobalamin

- 🌿 Synthetic, inactive form
- 🌿 Requires conversion to active forms and releases a small amount of cyanide during metabolism



Case 2 Findings

- 🌿 Address environmental stressors: Toxins, oxidative stress, and inflammation can elevate SAH and deplete methyl donors
- 🌿 Add exercise/movement: to support stress, energy and sleep
- 🌿 SAME supplementation??
 - 🌿 Starting at 200-400mg QD
 - 🌿 Titrate slowly
 - 🌿 Watch for anxiety, irritability, or insomnia (disturbed sleep)
 - 🌿 Consider COMT, MAOA
- 🌿 Recheck: 8–12 weeks
 - 🌿 Adjust based on response and tolerance

Case 3

Patient: 64 yom

Presenting Concerns: Anxiety and depression on and off for the past few decades, worse recently with stress of divorce. Known diagnosis of coronary artery disease (CAD), history of angina, and one prior angioplasty (2 years ago). Currently on statins and a beta blocker. Reports fatigue, mild cognitive slowing, and erectile dysfunction.

Medical History:

- Sedentary occupation
- Tries to eat healthy, veers towards SAD
- No tobacco use, occasional alcohol
- Strong paternal history of premature myocardial infarction (father deceased at 56). Brother with hypertension

Case 3

Methylation Profile; plasma

PRIMARY & INTERMEDIATE METABOLITES										
	RESULT/UNIT		REFERENCE INTERVAL		PERCENTILE					
					2.5 th	16 th	50 th	84 th	97.5 th	
Methionine	2.0	µmol/dL	1.6 -	3.6						
Cysteine	29	µmol/dL	20 -	38						
S-adenosylmethionine (SAM)	96	nmol/L	86 -	145						
S-adenosylhomocysteine (SAH)	37.3	nmol/L	10 -	22						
						68 th		95 th		
Homocysteine	11.4	µmol/L	<	11						
Cystathionine	0.02	µmol/dL	<	0.05						
METHYLATION INDEX										
	RESULT		REFERENCE INTERVAL		PERCENTILE					
					68 th		95 th			
SAM : SAH	2.6		>	4						

Case 3

- 🌱 **SAH:** 37.3 nmol/L (**97.5th percentile**; markedly elevated)
 - 🌱 Acts as an inhibitor of methyltransferases, impairing epigenetic regulation, neurotransmitter synthesis, and detox
- 🌱 **Homocysteine:** 11.4 $\mu\text{mol/L}$ (elevated; reference $<11 \mu\text{mol/L}$)
 - 🌱 Cardiovascular risk
- 🌱 **SAM:SAH Ratio: 2.6** (low; reference > 4)
 - 🌱 Indicates limited methyl donor availability
 - 🌱 **SAM is WNL**, therefore not an actionable item
- 🌱 Genetic Testing...

DNA Methylation Pathway Profile; Buccal Swab

GENE NAME / VARIATION	MUTATION NOT PRESENT	MUTATION(S) PRESENT	CALL
SHMT/C1420T	-/-		G
AHCY/1	-/-		A
AHCY/2	-/-		T
AHCY/19	-/-		A
MTHFR/C677T		+/+	T
MTHFR/A1298C	-/-		A
MTHFR/3	-/-		C
MTR/A2756G	-/-		A
MTRR/A66G		+/-	Hetero
MTRR/H595Y	-/-		C
MTRR/K350A	-/-		A
MTRR/R415T		+/-	Hetero
MTRR/S257T		+/-	Hetero
MTRR/11		+/-	Hetero
BHMT/1		+/+	T
BHMT/2	-/-		C
BHMT/4	-/-		A
BHMT/8		+/+	T
CBS/C699T	-/-		C
CBS/A360A		+/+	T
CBS/N212N	-/-		C
COMT/V158M		+/+	A
COMT/H62H		+/+	T
COMT/61		+/-	Hetero
SUOX/S370S	-/-		C
VDR/Taq1	-/-		C
VDR/Fok1	-/-		C
MAOA		+/+	T
NOS/D298E		+/-	Hetero
ACAT/1-02	-/-		G

Minus "-" represents no mutation

Plus "+" represents a mutation

"-/-" indicates there is no mutation

"+/-" indicates there is one mutation

"+/+" indicates there is a double mutation

Case 3

- 🌱 MTHFR/C677T: homozygous (TT)
 - 🌱 *Methylenetetrahydrofolate reductase* gene
 - 🌱 The C677T mutation results in a cytosine (C) being replaced by thymine (T) at position 677 of the MTHFR gene
 - 🌱 Leads to a thermolabile enzyme with reduced activity
 - 🌱 Impairs the conversion of 5,10-methylene-THF to 5-methyl-THF
- 🌱 NOS D298E (+/-): heterozygous
 - 🌱 *NOS3* gene, which encodes endothelial nitric oxide synthase (eNOS)
 - 🌱 Glutamate to aspartate may alter eNOS enzyme conformation, potentially reducing NO bioavailability
 - 🌱 Implicating vasodilation, platelet aggregation, and smooth muscle proliferation
 - 🌱 Increased risk of hypertension, coronary artery disease, and myocardial infarction

COMT & Methyl Donors

🌀 COMT +/- (V158M and H62H)

- 🌀 *Catechol-O-methyltransferase* gene
- 🌀 Two copies of the "slow" variants
- 🌀 Reduced COMT enzyme activity
 - 🌀 Slower clearance of dopamine, norepinephrine, and epinephrine
- 🌀 "Worrier": Tendency toward anxiety, rumination, or overstimulation
- 🌀 Difficulty recovering from stress
- 🌀 May be more sensitive to methyl donors
- 🌀 Magnesium, B2, B6, hydroxocobalamin or adenosylcobalamin
- 🌀 Stress management is key
- 🌀 Avoiding excess catechols (e.g., green tea extract, quercetin, EGCG)



Case 3

Findings:

- SNPs: MTHFR C677T, NOS, COMT +/-
- Functional: elevated SAH/homocysteine levels

Implications:

- Neurotransmitter imbalances: anxiety, depression
- Endothelial dysfunction: cardiovascular risk & hx of CAD
- Impaired detoxification and redox regulation: cellular stress

Recheck: 8–12 weeks

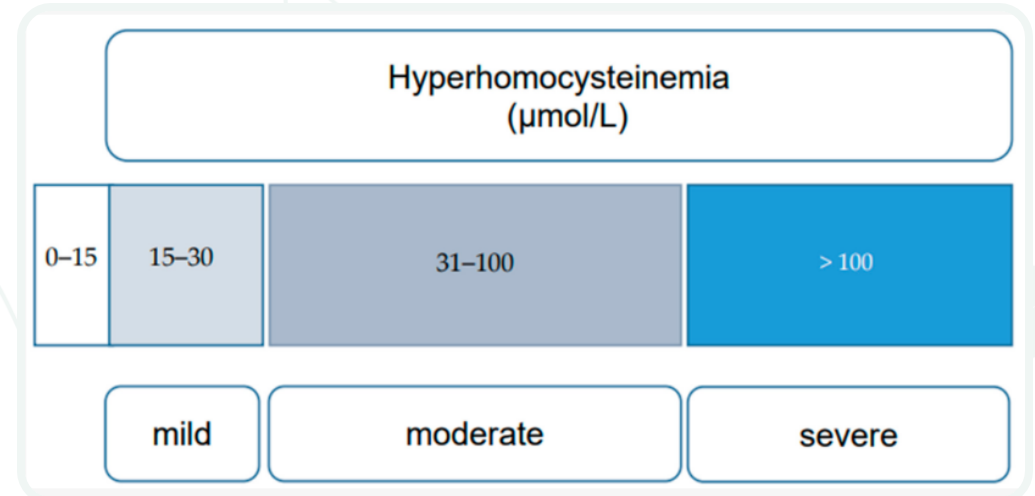
- Adjust based on response and tolerance

Case 3 Findings

- 🌱 Monitor and reduce SAH/homocysteine using B12/cobalamin, folate, B6
- 🌱 Support endothelial health
 - 🌱 Omega-3 fatty acids (EPA/DHA): Reduce inflammation, improve endothelial function, and lower triglycerides
- 🌱 Nutritional and lifestyle interventions targeting stress resilience, vascular support, and neurotransmitter balance
 - 🌱 Poor sleep reduces NO and raises endothelin-1, a vasoconstrictor
- 🌱 Comprehensive Cardiovascular Panel
- 🌱 Consider urinary neurotransmitter and salivary cortisol testing
- 🌱 Consider GSH testing

Integrating Methylation Testing into Practice

- Hyperhomocysteinemia:
 - Plasma levels above 15 $\mu\text{mol/L}$
 - Significant cardiovascular and neurological risk factor
 - Renal dysfunction, hypothyroidism, and certain medications (e.g., methotrexate, antiepileptics) can also elevate levels
 - Reassess after 8–12 weeks of intervention
- Chronic fatigue, mood disorders or cognitive decline
- ASD, neurodevelopmental delays
- Cardiovascular risk
- Detoxification considerations
- Recurrent miscarriage or fertility issues
- Aging or longevity optimization



Integrating Methylation Testing into Practice

🌱 Known SNPs:

- 🌱 *MTHFR C677T, A1298C, CBS, MTR, and MTRR* variants can impair homocysteine clearance

🌱 Nutrient deficiencies:

- 🌱 Low levels of B6, B12, folate, and riboflavin disrupt remethylation and transsulfuration pathways

Summary and Key Take-Aways

Methylation is a fundamental biochemical process that involves transferring a methyl group ($-CH_3$) to DNA, proteins, and other molecules

Involved in gene regulation, NT synthesis, detoxification, cardiovascular health, immune modulation, cellular repair and aging

A functional assessment of the Methylation Cycle is clinically relevant as methylation is individualized

Combining epigenetic biomarkers (methylation index) with DNA SNPs is warranted





**Thank you
and Questions?**