

Methylation & Memory Profiles in Serum

While minimally-invasive testing has been the hallmark of ZRT Laboratory for 20 years, the option to test in serum gives health care practitioners maximum choice and flexibility, allowing them to choose the best method to suit an individual patient's needs. Some analytes, e.g., ferritin and BDNF, can only be tested in serum. Serum tests have the advantage of being considered the clinical norm and are favored for insurance reimbursement.

For the assessment of analytes offered in our serum profiles, the patient must go to the phlebotomist first thing in the morning after an overnight fast (no food or drink except water for 10-12 hours). Several of the tests are nutrients so results would be affected by consumption of food or supplements containing these nutrients, and others are hormones that have peak values early in the morning.

Homocysteine, folate (vitamin B9), and vitamin B12 levels can help to evaluate methylation pathways that play essential roles in:

- DNA and RNA synthesis
- Methylation of DNA, neurotransmitters, and catechol estrogens
- Recycling of homocysteine to methionine
- Degradation of homocysteine to alpha-ketobutyrate for the Citric Acid Cycle
- Formation of cysteine, an amino acid essential for synthesis of the universal antioxidant glutathione

Production of methyl groups used in many of the above biochemical pathways is essential for health of the cardiovascular and nervous systems, and safe steroid hormone metabolism through methylation/inactivation of catechol estrogens.

We also include a test for Brain-Derived Neurotrophic Factor (BDNF), which helps nourish and regenerate healthy neurons in the central and peripheral nervous systems. BDNF present in serum is reflective of levels throughout the body, including the peripheral and central nervous systems. BDNF is regulated in part by the endocrine system, particularly estradiol, thyroid, and cortisol, thus making testing for steroid and thyroid hormones in concert with BDNF essential for evaluating nervous system health. All of the above play important roles in helping to prevent the progression of diseases of the brain associated with aging and memory loss, such as senile dementia and Alzheimer's disease.

Available Tests

Methylation Profile

Tests included: Ferritin, Folate, Homocysteine, Vitamin B12

Methylation & Memory – Basic Profile

Tests included: Estradiol, Progesterone, Testosterone, SHBG, TSH, Folate, Vitamin B12, Homocysteine, Brain-derived Neurotrophic Factor (BDNF)

Methylation & Memory – Advanced Profile

Tests included: Estradiol, Progesterone, Testosterone, DHEA-S, Cortisol, SHBG, TSH, Free T3, Free T4, TPOab, Ferritin, Folate, Vitamin B12, Homocysteine, BDNF

Note: Any of the serum tests listed in the profiles above can be ordered in any combination, or as individual tests added on to an existing serum profile.

Profiles Offered

PROFILE ▼	Sex & Adrenal Hormones						Thyroid Hormones				Iron Status	Methylation Indicators			BDNF
	E2	Pg	T	DS	C	SHBG	TSH	ft3	ft4	TPOab	FER	FOL	B12	HCY	
Methylation											•	•	•	•	
Methylation & Memory - Basic	•	•	•			•	•					•	•	•	•
Methylation & Memory - Advanced	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•

Methylation Profile

This profile comprises an assessment of nutrients involved as cofactors in the biosynthesis of neurotransmitters important for memory and brain function, and in the methylation processes that ensure the toxic compound homocysteine is converted to methionine. Methionine is in turn converted to S-adenosyl methionine, which serves to donate methyl groups to a variety of substrates involved in the synthesis and activation/inactivation of neurotransmitters, steroids (COMT/SAMe methylation/inactivation of catechol estrogens), proteins, and nucleic acids.

Methylation & Memory – Basic Profile

The Methylation and Memory Basic Profile gives an overview of the hormones and nutrients that, if deficient, can accelerate cardiovascular disease as well as memory loss, increasing risk for senile dementia and Alzheimer’s disease. This profile also includes BDNF, which is important for health of the central and peripheral nervous systems, and low levels are associated with higher risk for Alzheimer’s disease.

Methylation & Memory – Advanced Profile

The Methylation and Memory Advanced profile consists of the same analytes as the Basic Profile but additionally gives a broader overview of the adrenal and thyroid hormones and nutrients that, if deficient (e.g., DHEA-S, ft3, ft4, FER) or excessive (C, SHBG, TPOab), can accelerate cardiovascular disease and memory loss, increasing risk for cardiovascular events as well as senile dementia and Alzheimer’s disease.

Factors tested in the Memory & Methylation Profiles

Sex and Adrenal Hormones

For more information on hormones tested, please see our Provider Data Sheet on Female and Male Hormone Profiles in Serum. Also see under BDNF in this document for the relevance of hormone balance to adequate production of BDNF.

Thyroid Hormones

For more information on thyroid hormones, please see our Provider Data Sheet on Thyroid Profiles.

Vitamin B12, Folate, and Homocysteine

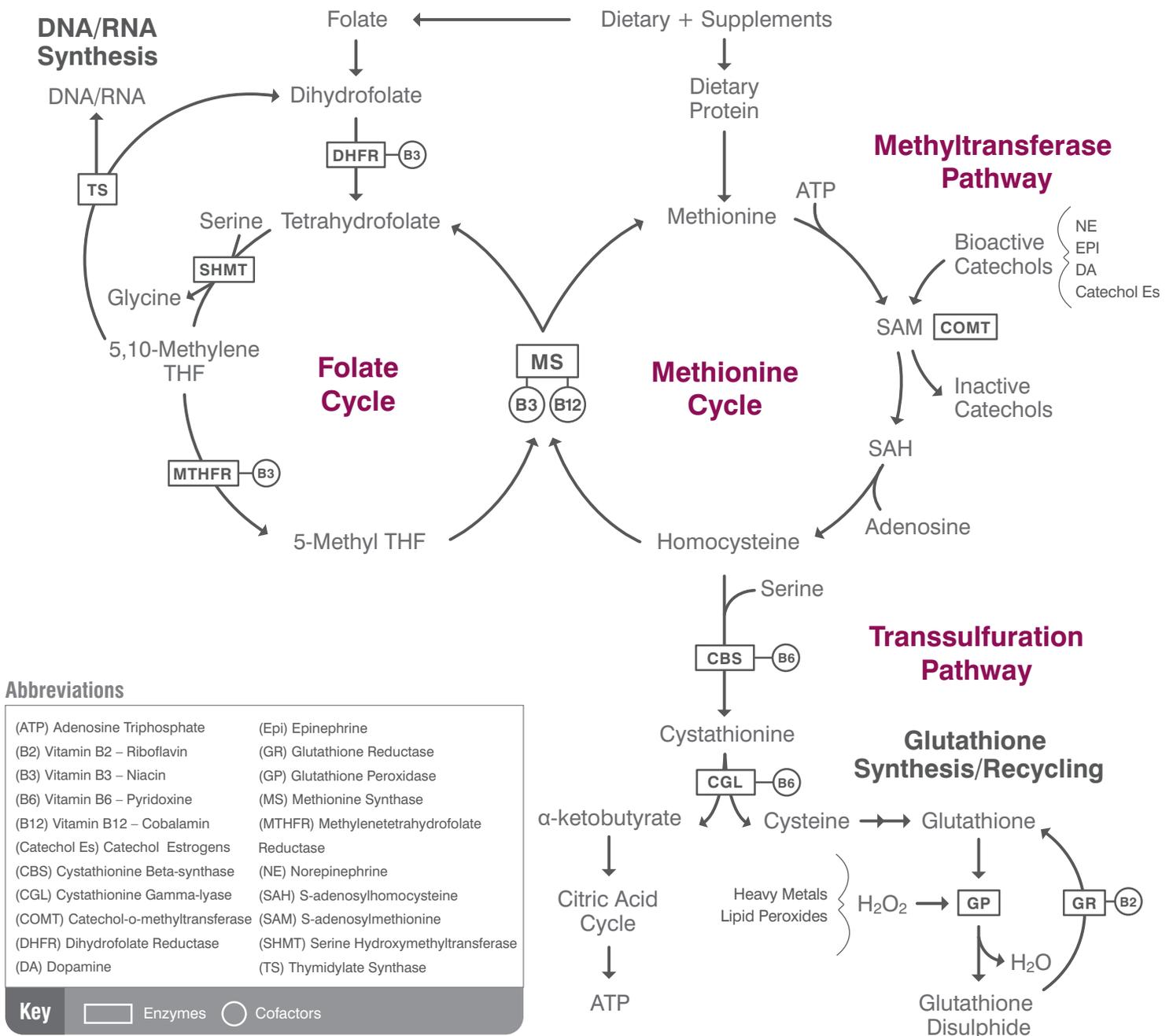
Folate (vitamin B9) and vitamin B12 are essential dietary requirements. Once ingested via the diet or supplementation they are stored in the liver. Folate is converted to its active form in the body, tetrahydrofolic acid, which along with Vitamin B12¹ is a cofactor for the conversion of homocysteine to the essential amino acid methionine. The diagram on the next page shows the interlinked folate and methionine cycles and the involvement of folate and vitamin B12.

In a healthy individual homocysteine is a short-lived intermediary amino acid that is toxic at high concentrations and must be removed quickly to prevent it from damaging the vascular system. Homocysteine is enzymatically converted back rapidly to methionine or cysteine, which prevents it from accumulating and becoming toxic in the bloodstream. Enzymes involved in converting homocysteine to less toxic and beneficial substrates for other metabolic pathways are highly dependent on the cofactor vitamins B12, folate, and B6. When the enzymes are defective (polymorphisms) or the vitamin cofactors are deficient, homocysteine accumulates (hyperhomocysteinemia).

Accumulation of homocysteine due to folate or vitamin B12 deficiency can lead to atherosclerosis² and is a risk factor for cardiovascular disease. High homocysteine has also been linked with cancer³ and possibly with neurodegenerative diseases⁴. Folate deficiency is linked with megaloblastic anemia and also with congenital neural tube defects (notably spina bifida), the risk of the latter being mitigated by folic acid supplements in pregnant women.

Serum folate and Vitamin B12 testing can indicate deficiency of these vitamins while homocysteine testing can show the abnormal accumulation of homocysteine, usually caused by a deficiency of vitamin B12 or folate. Very high levels of vitamin B12 can, paradoxically, be indicative of a functional vitamin B12 deficiency due to improper utilization⁵.

Methylation Pathways



Methylation Pathways Notes

In the re-methylation pathway recycling of homocysteine to methionine requires the enzymes methionine synthase (MS) and methyl tetrahydrofolate reductase (MTHFR) and the cofactor vitamins B12 and folate. Methionine is then converted to S-adenosyl methionine (S-AdoMet), which serves to donate methyl groups to a variety of substrates involved in the synthesis and activation/inactivation of neurotransmitters, steroids (COMT/S-AdoMet methylation/inactivation of catechol estrogens), proteins, and nucleic acids. The second pathway for removing homocysteine involves its conversion to cysteine through the Transsulfuration Pathway. Homocysteine is first converted to cystathionine by cystathionine-beta-synthase (CBS), an enzyme that requires vitamin B6 and serine. Cystathionine is then converted to cysteine via a lyase.

Both the transmethylation and transsulfuration metabolic pathways cross-regulate to maintain low levels of homocysteine and optimal levels of S-AdoMet and cysteine. For example, when S-AdoMet is low, CBS activity slows, and homocysteine is funneled more toward the transmethylation pathway requiring folate and vitamin B12 and the necessary enzymes MTHFR and MS to create S-AdoMet. When S-AdoMet is high it activates CBS, which funnels homocysteine metabolism more to the transsulfuration pathway for cysteine biosynthesis, helping to maintain adequate levels of glutathione.

Evaluation of the serum concentrations of B vitamin cofactors (B12 and folate) in combination with homocysteine, should help determine if dietary modification or B-vitamin supplementation may help reduce homocysteine levels and risk for damage to the cardiovascular system. Other contributors may include obesity, smoking, physical inactivity, diabetes, kidney failure and some medications such as cholesterol-lowering drugs, methotrexate, and nicotine.

Ferritin

Circulating ferritin is important for the storage and transport of iron in the body, thereby maintaining a stable supply of iron for hemoglobin synthesis. Elevated serum ferritin, representing iron excess, closely correlates with cardiovascular disease risk factors such as triglyceride and HDL-cholesterol levels, insulin resistance, and high BMI⁶. Iron metabolism is associated with oxidative stress and lipid peroxidation, contributing to dyslipidemia. It is an important emerging biomarker for cardiovascular disease risk, particularly when combined with cardiometabolic markers such as lipid profiles and fasting insulin; it has been found to relate to a clustering of metabolic disorders in non-diabetic elderly individuals⁷. Ferritin is also an acute phase reactant protein and is elevated in chronic inflammatory illness and acute infections⁸, as well as in people with liver damage⁹. On the other hand, iron deficiency anemia is associated with both overt and subclinical hypothyroidism¹⁰. The iron-containing enzyme thyroid peroxidase is required for synthesis of thyroid hormones. Iron is also an important cofactor in the synthesis of the neurotransmitters dopamine and serotonin. A low serum ferritin level indicates low iron stores and is diagnostic of iron-deficiency anemia.

BDNF

Brain-derived neurotrophic factor (BDNF) supports the viability of neurons, promotes growth and differentiation of new neurons, and is involved in the control of synaptic function and synaptic plasticity¹¹. It plays an important role in the pathophysiology of neurological disorders, and alterations in circulating levels have been reported in major depression, bipolar disorder, Alzheimer's disease, Huntington's disease and Parkinson's disease^{12,13}. Serum levels of BDNF have been proposed as a biomarker for mood disorders¹⁴. Sex hormones like estradiol and testosterone promote neurogenesis and improve cognitive function while stress hormones like cortisol have the opposite effect and lower BDNF and its receptors¹⁵. Estrogens augment the actions of BDNF by stimulating the synthesis of both BDNF and tropomyosine receptor kinase (TrkB). Keeping hormones, especially estrogens in women and testosterone in men, within healthy physiological ranges should help maintain optimal BDNF levels and stave off aging of the central and peripheral nervous systems.

BDNF is not only produced by neurons but also found in blood platelets, from which it is released during blood coagulation; it is therefore readily detectable in serum, reflecting brain levels¹⁶.

Relevant Provider Data Sheets

- ▶ Thyroid Profiles
- ▶ Female & Male Hormone Profiles in Serum

References

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