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

### Methylation Status

<table>
<thead>
<tr>
<th>Methylation</th>
<th>Downregulating SNPs</th>
<th>Upregulating SNPs</th>
<th>Transsulfuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homocysteine</td>
<td>MTHFR C677T, A1298C</td>
<td>MTR A2756G, CBS</td>
<td>Serine ▲</td>
</tr>
<tr>
<td>SAH</td>
<td>COMT V158M</td>
<td>CBS</td>
<td></td>
</tr>
<tr>
<td>Methionine</td>
<td>MTRR A66G</td>
<td>C699T, BHMT</td>
<td></td>
</tr>
<tr>
<td>Choline</td>
<td>MAT1A D18777A</td>
<td>C1289T, GNMT</td>
<td></td>
</tr>
<tr>
<td>Sarcosine</td>
<td>SHMT1 C1240T</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Interpretation At-a-Glance

- Methylation
  - Homocysteine ▲
  - SAH ▲
  - Methionine ▲
  - Choline ▲
  - Sarcosine ▲

- Genetic Polymorphism
  - **Downregulating SNPs**
    - MTHFR C677T, A1298C
    - COMT V158M
    - MTRR A66G
    - MAT1A D18777A
    - SHMT1 C1240T
  - **Upregulating SNPs**
    - MTR A2756G, CBS
    - C699T, BHMT
    - C1289T, GNMT

- Transsulfuration
  - Serine ▲

### Metabolite Balance

- **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 & Colormetric

Results
micromol/L

<table>
<thead>
<tr>
<th>Ratios</th>
<th>Quintile Distribution</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Methylation Index (SAM/SAH Ratio)</td>
<td>3.3</td>
<td>2.2-6.4</td>
</tr>
<tr>
<td>2. Methylation Balance Ratio</td>
<td>1.08</td>
<td>1.03-1.20</td>
</tr>
<tr>
<td>3. Met/Sulf Balance Ratio</td>
<td>0.62</td>
<td>0.55-0.64</td>
</tr>
<tr>
<td>4. Betaine/Choline Ratio</td>
<td>2.3</td>
<td>2.6-7.7</td>
</tr>
</tbody>
</table>

Methyl Group Donors

<table>
<thead>
<tr>
<th>Ratios</th>
<th>Quintile Distribution</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>5. S-adenosylmethionine (SAM)</td>
<td>109</td>
<td>65-150 nanomol/L</td>
</tr>
<tr>
<td>6. Methionine</td>
<td>36</td>
<td>23-38</td>
</tr>
<tr>
<td>7. Choline</td>
<td>19.1</td>
<td>5.2-13.0</td>
</tr>
<tr>
<td>8. Betaine</td>
<td>44</td>
<td>21-71</td>
</tr>
<tr>
<td>9. Serine</td>
<td>147</td>
<td>91-161</td>
</tr>
</tbody>
</table>

Methyl Group Metabolites

<table>
<thead>
<tr>
<th>Ratios</th>
<th>Quintile Distribution</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>10. S-adenosylhomocysteine (SAH)</td>
<td>33</td>
<td>16-41 nanomol/L</td>
</tr>
<tr>
<td>11. Homocysteine †</td>
<td>11.3</td>
<td>3.7-10.4</td>
</tr>
<tr>
<td>12. Dimethylglycine (DMG)</td>
<td>2.9</td>
<td>1.6-5.0</td>
</tr>
<tr>
<td>13. Sarcosine</td>
<td>6,368</td>
<td>3,670-6,743 nanomol/L</td>
</tr>
<tr>
<td>14. Glycine</td>
<td>267</td>
<td>181-440</td>
</tr>
</tbody>
</table>

Transsulfuration Metabolites

<table>
<thead>
<tr>
<th>Ratios</th>
<th>Quintile Distribution</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>15. Cystathionine</td>
<td>216</td>
<td>74-369 nanomol/L</td>
</tr>
<tr>
<td>16. Cyst(e)ine</td>
<td>323</td>
<td>271-392</td>
</tr>
<tr>
<td>17. Taurine</td>
<td>83</td>
<td>50-139</td>
</tr>
<tr>
<td>18. Glutathione †</td>
<td>1,577</td>
<td>&gt;=669</td>
</tr>
</tbody>
</table>
Methylation / Transsulfuration Pathway

**Folate Cycle**

- **Thymidylate** (THF)
- **Serine**
- **Glycine**
- **5-MTHF**
- **5,10-MTHF**
- **MTHFR**

**Methylation**

- **MTR**
- **MTRR**
- **B12**
- **SAM, B2, B3**
- **SAM**
- **MT
- **GNMT**
- **MT
- **B3**
- **AHCY**

**Main Pathway**

- **SAM**
- **MTR**
- **B12**
- **SAM**
- **MT
- **B3**
- **AHCY**

**Backup Pathway**

- **MT**
- **B3**
- **AHCY**

**Enzyme**

- **MTR**
- **B12**
- **B3**

**Cofactors**

- **B6, Fe**
- **Zn**

**Main Pathway**

- **THF**
- **5-MTHF**
- **5,10-MTHF**
- **SHMT**

**Detoxification**

- **Pyruvate**
- **Glycine**
- **Sarcosine**
- **Glutathione**
- **Cysteine**
- **Homocysteine**
- **B12**
- **Serine**
- **SAM**
- **Glycine**
- **5,10-MTHF**
- **MTHFR**

**Energy Production**

- **Pyruvate**
- **Glycine**
- **Sarcosine**
- **Glutathione**
- **Cysteine**
- **Homocysteine**
- **B12**
- **Serine**
- **SAM**
- **Glycine**
- **5,10-MTHF**
- **MTHFR**
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.

### Health Implications
- 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.¹,²
- Homozygosity for 677 (+/+) results in 60-70% reduction in MTHFR enzyme activity. Heterozygosity for 677 (-/+) results in 30-40% reduction in MTHFR enzyme activity.³
- Lower levels of B-vitamin and folate increase the risk of elevated homocysteine related to MTHFR SNPs.²
- Homozygous C677T subjects have higher Hcy levels, while heterozygous subjects have mildly raised Hcy levels compared to controls.⁴
- MTHFR C677T SNPs have been associated with many disease processes including:
  - Cardiovascular disease ⁵⁻⁷
  - Depression and schizophrenia ⁶,⁹
  - Increased risk of birth defects and Down’s syndrome ¹⁰
  - Psoriasis
  - Diabetes
  - Parkinson’s disease

### 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.¹¹
- Evaluate the status of vitamin B-2 and B-3 (MTHFR enzyme cofactors).

### References

### Frequency

<table>
<thead>
<tr>
<th>Population Category</th>
<th>CC</th>
<th>CT</th>
<th>TT</th>
</tr>
</thead>
<tbody>
<tr>
<td>EUR</td>
<td>47%</td>
<td>44%</td>
<td>9%</td>
</tr>
<tr>
<td>EAS</td>
<td>37%</td>
<td>47%</td>
<td>16%</td>
</tr>
<tr>
<td>AFR</td>
<td>81%</td>
<td>19%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>AMR</td>
<td>32%</td>
<td>52%</td>
<td>16%</td>
</tr>
<tr>
<td>SAS</td>
<td>68%</td>
<td>30%</td>
<td>2%</td>
</tr>
</tbody>
</table>

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

EAS (East Asian): Han Chinese (Beijing), Japanese (Tokyo), Southern Han Chinese, Chinese Dai, Kin (Vietnam)

EUR (European): Americans with Northern and Western European Ancestry, Toscani, Finnish, British, Spanish

AFR (African): Nigerian, Kenyan, Gambian, Mendi (Sierra Leone), African Americans, African Caribbeans

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