Methylenetetrahydrofolate Reductase (MTHFR) 2 Variants

**Indications for Ordering**
Determine genetic contribution to hyperhomocysteinemia

**Contraindications for Ordering**
Testing not recommended for
- Recurrent pregnancy loss
- Thrombophilia screening
- Neural tube defect risk assessment
- Testing family members of individuals with identified MTHFR variants

**Test Description**
- PCR followed by fluorescence monitoring
- Variants detected
  - c.665C>T; p.Ala222Val (legacy name c.677C>T)
  - c.1286A>C; p.Glu429Ala (legacy name c.1298A>C)

**Tests to Consider**

**Typical Testing Strategy**

**Homocysteine, Total 0099869**
- Initial testing for hyperhomocysteinemia

**Methylenetetrahydrofolate Reductase (MTHFR) 2 Variants 0055655**
- Determine genetic contribution to hyperhomocysteinemia for individuals with elevated plasma homocysteine

**Related conditions**
- Hyperhomocysteinemia
  - Multifactorial causation – a combination of genetic, physiologic, and environmental factors
  - Homozygosity for the MTHFR c.665C>T variant is a genetic risk factor
  - Possible risk factor for cardiovascular disease and venous thrombosis
  - Folic acid supplementation reduces homocysteine levels but effect on cardiovascular risk or mortality is uncertain
- Thrombophilia
  - Elevated homocysteine and homozygosity for the c.665C>T variant may be associated with a mild increase (1.27) risk for venous thromboembolism

**Genetics**
**Gene – MTHFR**

**Inheritance** – autosomal recessive

**Variants/function – MTHFR gene variants (c.665C>T and c.1286A>C) may reduce MTHFR enzyme activity**
- MTHFR enzyme is involved in folate metabolism
  - Catalyzes 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate
  - Necessary cofactor for the remethylation of homocysteine
  - Reduced enzyme function may contribute to mild to moderate increases in plasma homocysteine

**Test Interpretation**

**Sensitivity/specificity**
- Clinical sensitivity – unknown
- Hyperhomocysteinemia caused by genetic, physiologic, and environmental factors
- MTHFR variants are only one contributing factor
- Analytical sensitivity/specificity – 99%

**Prevalence**
- Allelic frequency
  - c.665C>T
    - Hispanics – 0.5
    - European Caucasians – 0.35
    - African Americans – 0.12
  - c.1286A>C
    - European Caucasians – 0.31
    - African Americans – 0.15
- Homozygosity for c.665C>T is 1-15% in the U.S. overall and 25% in Hispanics
Results

- Positive
  - Homozygosity for c.665C>T
    - Associated with moderate reduction in enzyme activity and increased plasma homocysteine levels
  - Homozygosity for c.1286A>C
    - Associated with clinically insignificant reduction in enzyme activity
  - Compound heterozygosity (c.665C>T/c.1286A>C)
    - Associated with clinically insignificant reduction in enzyme activity
  - Heterozygosity for either c.665C>T or c.1286A>C
    - Associated with clinically insignificant reduction in enzyme activity
- Negative – no variants detected
  - Neither of the common MTHFR gene variants tested, c.665C>T or c.1286A>C, was detected
  - Genotype is associated with a normal folate metabolism

Limitations

- Only two MTHFR gene variants (c.665C>T and c.1286A>C) are tested
- Other causes for hyperhomocysteinemia are not addressed
- Diagnostic errors can occur due to rare sequence variations

Reference