# Test Definition: MTHP

MTHFR 2 Mutations Analysis, B

## Overview

### Useful For

Direct mutation analysis for the *MTHFR* C677T and/or A1298C mutations should be reserved for patients with coronary artery disease, acute myocardial infarction, peripheral vascular artery disease, stroke, or venous thromboembolism who have increased basal homocysteine levels or an abnormal methionine-load test.

### Genetics Test Information

Tests for C677T and A1298C mutations only.

### Profile Information

| Test ID | Reporting Name | Available Separately | Always Performed |
|---|---|---|---|
| MTHFR | MTHFR C677T Mutation Analysis, B | Yes | Yes |
| MTHAC | MTHFR A1298C Mutation Analysis, B | Yes | Yes |

### Testing Algorithm

When this test is ordered, *MTHFR* and *MTHAC* mutations will always be performed together.

### Special Instructions

- Informed Consent for Genetic Testing
- Coagulation Patient Information
- Informed Consent for Genetic Testing (Spanish)

### Method Name

Direct Mutation Analysis

### NY State Available

Yes

## Specimen

### Specimen Type

Whole blood

### Advisory Information

Can be combined with other molecular coagulation tests:

-MTHAC / 5,10-Methylenetetrahydrofolate Reductase A1298C, Mutation, Blood

-F5DNA / Factor V Leiden (R506Q) Mutation, Blood

-PTNT / Prothrombin G20210A Mutation, Blood

-MTHFR / 5,10-Methylenetetrahydrofolate Reductase C677T, Mutation, Blood

## Specimen Required

**Container/Tube:**

**Preferred:** Yellow top (ACD solution B)

**Acceptable:** Lavender top (EDTA) or blue top (sodium citrate)

**Specimen Volume:** Full tube

**Collection Instructions:**

1. Invert several times to mix blood.

2. Send specimen in original tube.

## Forms

1. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available in Special Instructions:

-Informed Consent for Genetic Testing (T576)

-Informed Consent for Genetic Testing-Spanish (T826)

2. Coagulation Patient Information (T675) in Special Instructions

## Specimen Minimum Volume

1 mL blood in a 3 mL ACD tube

## Reject Due To

| | |
|---|---|
| Gross hemolysis | OK |
| Gross lipemia | OK |
| Other | Extracted DNA |

## Specimen Stability Information

| Specimen Type | Temperature | Time | Special Container |
|---|---|---|---|
| Whole blood | Ambient (preferred) | 7 days | |
| | Frozen | 14 days | |
| | Refrigerated | 14 days | |

# Clinical and Interpretive

## Clinical Information

Hyperhomocysteinemia is an independent risk factor for coronary artery disease, acute myocardial infarction,

peripheral arterial disease, stroke, and venous thromboembolism. Homocysteine is a sulfhydryl-containing amino acid formed as an intermediary during the conversion of methionine to cystathionine. Genetic or nutrition-related disturbances (eg, deficiency of vitamins B12, B6, and folic acid) may impair the transsulfuration or remethylation pathways of homocysteine metabolism and cause hyperhomocysteinemia. The enzyme MTHFR catalyzes reduction of 5,10-methylene tetrahydrofolate to 5-methyl tetrahydrofolate, the major form of folate in plasma; 5-methyl tetrahydrofolate serves as a methyl donor for remethylation of homocysteine to methionine. Patients with severe MTHFR deficiency (enzymatic activity 0%-20% of normal) develop homocysteinuria, a severe disorder with a wide range of associated clinical manifestations, including developmental delay, mental retardation, and premature vascular disease. Seven unique *MTHFR* mutations have been associated with homocysteinuria, all among patients who were either homozygous or compound heterozygotes for 1 or more of these mutations.

A milder deficiency of MTHFR, with approximately 50% residual enzyme activity and marked enzyme lability to heat inactivation, is associated with a cytosine to thymine mutation at nucleotide position 677, encoding for an alanine-223 to valine substitution (*MTHFR* C677T). A second mutation in *MTHFR* exon 7, A1298C, results in a conversion of a glutamic acid codon to an alanine codon. The *MTHFR* A1298C mutation reduces MTHFR activity to a lesser extent than C677T, but compound heterozygous *MTHFR* A1298C/C677T may develop hyperhomocysteinemia.

For suspected hyperhomocysteinemia, we recommend that a basal plasma homocysteine level be measured. Vitamin B12, B6, and folic acid levels should be measured in patients with hyperhomocysteinemia.

## Reference Values

Negative

## Interpretation

The interpretive report will include specimen information, assay information, background information, and conclusions based on the test results (negative, heterozygous *MTHFR* C677T, homozygous *MTHFR* C677T; negative, heterozygous *MTHFR* A1298C, homozygous *MTHFR* A1298C).

## Cautions

Direct mutation analysis for the *MTHFR* C677T and/or A1298C mutations in an asymptomatic family member with a normal basal homocysteine level is not useful.

For Mayo Clinic patients, Cardiovascular, Vascular, Thrombophilia Center, Special Coagulation Clinic, and Medical Genetics consultations and counseling are available for questions regarding DNA diagnostic testing, test interpretation, and patient management, and may be especially helpful in complex cases.

Neither the *MTHFR* A1298C nor the C677T mutation test detects other causes of hyperhomocysteinemia, such as occur with other mutations within the *MTHFR* gene or the cystathionine beta-synthase gene. In addition, the *MTHFR* gene mutation may not be present when hyperhomocysteinemia is due to acquired disorders, such as deficiency of vitamins B12, B6, or folic acid; chronic renal failure; zinc deficiency; leukemia; psoriasis; or antifolate drug therapy.

## Supportive Data

The *MTHFR* C677T mutation is not an independent risk factor for coronary artery disease or venous thromboembolism in the absence of hyperhomocysteinemia. Homozygosity for the mutant allele confers an increased risk of hyperhomocysteinemia when vitamin deficiency is present, especially folic acid. Heterozygosity for the mutant allele confers no risk for hyperhomocysteinemia and does not warrant intervention.

## Clinical Reference

1. Rees MM, Rodgers GM: Homocysteinemia: association of a metabolic disorder with vascular disease and thrombosis. Thromb Res 1993;71:337-359

2. Frosst P, Blom HF, Goyette P, et al: A candidate gene risk factor for vascular disease: a common mutation in

methylenetetrahydrofolate reductase. Nature Genet 1995;10:111-113

3. Ma J, Stampfer MJ, Hennekens CH, et al: Methylenetetrahydrofolate reductase polymorphism, plasma folate, homocysteine, and risk of myocardial infarction in US physician. Circulation 1996;94:2410-2416

4. Deloughery TG, Evans A, Sadeghi A, et al: Common mutation in methylenetetrahydrofolate reductase: correlation with homocysteine metabolism and late-onset vascular disease. Circulation 1996;94:3074-3078

5. Heit JA: Thrombophilia: clinical and laboratory assessment and management. In Consultative Hemostasis and Thrombosis. Fourth edition. Edited by CS Kitchens, BM Alving, CM Kessler. Saunders, 2012

## Performance

### Method Description

Direct mutation analysis using PCR amplification, signal generation, and release by cleavage of sequence-specific alleles.(Invader MTHFR 677, Invader MTHFR 1298, Invader Plus Chemistry, Hologic, Madison, WI)

### PDF Report

No

### Day(s) and Time(s) Test Performed

Monday through Friday; 12 p.m.

### Analytic Time

3 days

### Maximum Laboratory Time

5 days

### Specimen Retention Time

Whole blood stored 2 weeks

### Performing Laboratory Location

Rochester

## Fees and Codes

### Fees

- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their Regional Manager. For assistance, contact Customer Service.

### Test Classification

This test has been modified from the manufacturer's instructions. Its performance characteristics were determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

### CPT Code Information

81291

## LOINC® Information

| Test ID | Test Order Name | Order LOINC Value |
|---|---|---|
| MTHP | MTHFR 2 Mutations Analysis, B | 38415-6 |

| Result ID | Test Result Name | Result LOINC Value |
|---|---|---|
| 21827 | Methylenetetrahydrofol Reduc Mut, B | 28005-7 |
| 34701 | MTHFR A1298C Mutation Analysis, B | 28060-2 |
| 34702 | MTHAC Interpretation | 69047-9 |
| 21828 | MTHFR Interpretation | 69049-5 |
| 21830 | MTHFR Reviewed By | 18771-6 |
| 34703 | MTHAC Reviewed By | 18771-6 |