Medical Policy

Genetic Testing for Hereditary Thrombophilia

Policy Number: OCA 3.728
Version Number: 6
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Product Applicability

<table>
<thead>
<tr>
<th>Well Sense Health Plan</th>
<th>Boston Medical Center HealthNet Plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>☑ New Hampshire Medicaid</td>
<td>☑ MassHealth</td>
</tr>
<tr>
<td>☑ NH Health Protection Program</td>
<td>☑ Qualified Health Plans/ConnectorCare/Employer Choice Direct</td>
</tr>
<tr>
<td></td>
<td>☑ Senior Care Options ◊</td>
</tr>
</tbody>
</table>

Notes:
+ Disclaimer and audit information is located at the end of this document.
◊ The guidelines included in this Plan policy are applicable to members enrolled in Senior Care Options only if there are no criteria established for the specified service in a Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD) or local coverage determination (LCD) on the date of the prior authorization request. Review the member’s product-specific benefit documents at www.SeniorsGetMore.org to determine coverage guidelines for Senior Care Options.

Policy Summary

The Plan considers genetic testing for hereditary thrombophilia to be medically necessary to identify predisposition to thrombosis when Plan criteria are met. **Plan prior authorization is required for all molecular and chromosomal genetic testing** except for prenatal genetic screening tests for a member with one of the pregnancy diagnosis codes specified in the Applicable Coding section of the Genetic Testing Guidelines and Pharmacogenetics medical policy (policy number OCA 3.7272), Chromosomal Microarray Analysis for Unexplained Intellectual Disabilities and/or Multiple Congenital Anomalies medical policy (policy number OCA 3.573), or Genetic Testing for Fragile X-Associated Disorders medical policy (policy number OCA 3.571) when applicable Plan criteria are met. Biochemical genetic tests used to study the amount or activity level of proteins to indicate changes to the DNA require prior

Genetic Testing for Hereditary Thrombophilia

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authorization only when the test is included in the Applicable Coding section of a Plan genetic testing medical policy.

The Plan supports the National Comprehensive Cancer Network (NCCN) guidelines for genetic counseling for all genetic tests conducted with Plan members; NCCN recommends that adequate pre-test and post-test genetic counseling be provided by a health care professional with expertise in genetics. Genetic counseling provided to a Plan member (and/or guardian if the member is under the age of 18) should be documented in the member’s medical record and conducted by an appropriately trained practitioner with expertise and experience in genetics, including a provider acting within the scope of his/her license and practice, clinical geneticist, or genetic counselor.

It will be determined during the Plan’s prior authorization process if the service is considered experimental and investigational for the requested use. See the Plan’s policy, Experimental and Investigational Treatment (policy number OCA 3.12), for the product-specific definitions of experimental or investigational treatment. See the following Plan policies available at www.bmchp.org for BMC HealthNet Plan members (or at www.SeniorsGetMore.org for Senior Care Options members) and www.wellsense.org for Well Sense Health Plan members for additional prior authorization guidelines for genetic testing:

1. Chromosomal Microarray Analysis for Unexplained Intellectual Disabilities and/or Multiple Congenital Anomalies, policy number OCA 3573
2. Gene Expression Profiling of Tumor Tissue to Predict Cancer Recurrence and Risk Stratification (Including Oncotype DX™ and Other Tests), policy number OCA 3.572
3. Genetic Testing for Familial Malignant Melanoma, policy number OCA 3.78
4. Genetic Testing for Fragile X-Associated Disorders, policy number OCA 3.571
5. Genetic Testing Guidelines and Pharmacogenetics, policy number OCA 3.727
6. Genetic Testing for Hereditary Breast and Ovarian Cancer Syndrome, policy number OCA 3.57
7. Genetic Testing for Hereditary Colorectal Cancer, policy number OCA 3.64
8. Preimplantation Genetic Testing (Preimplantation Genetic Diagnosis and Pregenetic Screening), policy number OCA 3.726

Description of Item or Service

Molecular Genetic Testing for Hereditary Thrombophilia: Molecular genetic tests that identify genetic variant defects associated with a predisposition to thrombosis. A genetic susceptibility to thrombosis in combination with other risk factors increases the individual’s risk of venous thromboembolism (VTE).
Genetic testing for gene variants associated with thrombophilias include testing of factor V Leiden, prothrombin gene G20210A, and the methylenetetrahydrofolate reductase (MTHFR) C677T gene. See the Medical Policy Statement section and the Limitations section of this policy for Plan criteria and prior authorization guidelines for these tests. (Guidelines for factor V Leiden and prothrombin gene G20210A testing to determine predisposition to thrombosis are outlined in the Medical Policy Statement section. Criteria for methylenetetrahydrofolate reductase (MTHFR) C677T genetic testing to diagnose hereditary thrombophilia are specified in the Limitations section of this Plan policy.)

**Thrombophilia Panel:** In addition to the molecular genetic tests specified above, a thrombophilia panel may include the following biochemical genetic tests, coagulation tests, and antibody screening tests (that do NOT require Plan prior authorization).

1. Protein C activity level
2. Protein S activity level
3. Antithrombin III activity (recommended for recurrent VTE)
4. Antiphospholipid antibody screening (including Lupus anticoagulant, anticardiolipin antibodies, and beta 2 glycoprotein antibodies) to rule out acquired thrombophilia

In selected high risk obstetric or VTE patients or those with a striking family history of thrombosis, additional testing under the direction of a hematologist, perinatologist or clinical geneticist may be indicated.

**Medical Policy Statement**

Genetic testing for inherited thrombophilia is considered medically necessary when ALL of the following applicable Plan criteria are met and documented in the member’s medical record, as specified below in items 1 through 3:

1. The result of the testing will directly impact the treatment being delivered to the member; AND

2. Member has at least ONE (1) of the following medical conditions, as specified below in item a or item b:

   a. Member has at least ONE (1) of the following **obstetric complications**, as listed below in items (1) through (6):

      (1) Recurrent pregnancy loss (i.e., 2 or more lost pregnancies); OR

      (2) Early onset preeclampsia; OR

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(3) Placental abruption; OR

(4) Severe intrauterine growth restriction (IUGR); OR

(5) Placental abnormality related to vascular underperfusion; OR

(6) Perinatal arterial ischemic stroke (and would include testing for maternal and infant thrombophilias); OR

b. Member has a **personal history** of single or multiple venous thromboembolism (VTE) of **unknown etiology** and at least ONE (1) of the following criteria is met, as specified below as item (1) or item (2):

(1) Member has had a VTE of unknown etiology **before age 50** (with or without a family history of known thrombophilia or thrombosis, i.e., VTE or pulmonary embolism); OR

(2) Member has had a VTE of unknown etiology **(at any age)** and meets at least ONE (1) of the following criteria, as specified below in item (a) or item (b):

   (a) Member has at least ONE (1) first-degree relative with a documented genetic thrombophilia diagnosis; OR

   (b) Member has at least ONE (1) first-degree relative with a history of thrombosis (VTE or pulmonary embolism) of presumed unknown etiology before age 50; AND

3. ONE (1) or more of the following molecular genetic tests will be conducted as part of a thrombophilia panel (and does require Plan prior authorization):

   a. Factor V Leiden (FVL) gene variant DNA analysis (p.Arg506Gln); AND/OR

   b. Prothrombin gene G20210A DNA analysis

**Limitations**

1. Genetic testing for hereditary thrombophilia is considered experimental and investigational when Plan criteria are not met (with criteria specified in the Medical Policy Statement section of this policy). Prior authorization requests that do not meet Plan criteria require Plan Medical Director review and approval, including but not limited to ANY of the following conditions/indications, as specified below in items a through f:
a. Testing of a member when the indication is related to oral contraceptive use (when Plan criteria are not met); OR

b. Testing for a member with his/her first venous thromboembolism (VTE) less than age 50 years of age with a known etiology unrelated to thrombophilia;‡ OR

‡ Note: Examples of a VTE etiology unrelated to hereditary thrombophilia may include trauma or cancer only when the condition is the known cause of the member’s thrombophilia or thrombosis.

c. Testing for a member age 50 years of age or older with his/her first venous thromboembolism (VTE) with a known etiology unrelated to thrombophilia, and the member has no family history of recurrent VTE;‡ OR

‡ Note: Examples of a VTE etiology unrelated to hereditary thrombophilia may include trauma or cancer only when the condition is the known cause of the member’s thrombophilia or thrombosis.

d. Testing for an asymptomatic member with or without a family history of recurrent VTE; OR

e. Testing of a member when the indication is related to hormonal replacement therapy (and Plan criteria are not met); OR

f. General population screening.

2. Genetic testing of methylenetetrahydrofolate reductase (MTHFR) to diagnose hereditary thrombophilia is considered experimental and investigational.

3. Factor V HR2 haplotype (F5 HR2) variant testing is considered experimental and investigational to determine thrombophilia, including reflex testing of F5 HR2 following identification of member with the F5 p.Arg506Gln (FVL) variant.

4. Genetic testing that is marketed directly to consumers (direct-to-consumer or DTC) that are ordered by a member without the order of a treating health care provider is not covered.

5. Genetic testing for hereditary thrombophilia requires Plan Medical Director review when a member has had recurrent VTEs or had a VTE in unusual sites, the treating provider recommends testing, and Plan criteria are not met.

6. Factor V Leiden testing is considered not medically necessary for ANY of the following indications, as specified below in items a through c:

a. Routine testing during pregnancy; OR
b. Prenatal and newborn screening; OR

c. Testing of individuals with arterial thrombosis; OR ◊

◊ Note: A member with arterial thrombosis should be screened for antiphospholipid antibodies. The antiphospholipid syndrome (APS) is characterized by thrombosis, recurrent fetal death, and the presence of circulating antiphospholipid antibodies. An individual with APS has an increased risk for both venous and arterial thrombosis.

7. Prior authorization requests for Factor V Leiden testing of neonates or children with catheter-related thrombosis require Plan Medical Director review and approval.

8. Multigene Panel Testing:

The use of a multigene testing panel is generally considered to be NOT medically necessary as an alternative to, or in addition to, factor V Leiden and prothrombin gene G20210A testing due to limited data on clinical validity and clinical utility of multigene testing. If the treating provider is recommending multigene panel testing rather than, or in addition to, the condition-targeted testing specified in the Medical Policy Statement section, Plan Medical Director review is required. For multigene panel testing to be considered medically necessary, medical record documentation must be submitted to the Plan with the prior authorization request demonstrating that ALL of the following criteria are met (and after approval by a Plan Medical Director), with criteria specified below in items a through g:

a. A recommendation for multigene panel testing for the member by an independent board-certified or board-eligible Medical Geneticist, an American Board of Medical Genetics or American Board of Genetic Counseling-certified Genetic Counselor not employed by a commercial genetic testing laboratory, or a genetic nurse credentialed as either a Genetic Clinical Nurse (GCN) or an Advanced Practice Nurse in Genetics (APGN) by either the Genetic Nursing Credentialing Commission (GNCC) or the American Nurses Credentialing Center (ANCC) who is not employed by a commercial genetic testing laboratory; this provider has a documented evaluation of the member which includes a completed 3-generation pedigree and intends to engage in post-test follow-up counseling; AND

b. Member meets criteria for genetic testing outlined in the Medical Policy Statement section of this policy AND

c. All genes included in the multigene panel are relevant to the personal medical history, biological family medical history, and/or treatment plan for the member being tested and there are professional society management guidelines or National Comprehensive Cancer Network (NCCN) guidelines (with applicable references provided

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with the prior authorization request) documenting the clinical utility of testing for the members who test positive for any and all genes in the panel; AND

d. The results of the requested multigene panel will directly impact the treatment plan and clinical decision-making process for the member being tested; AND

e. There are no other known causative circumstances or factors (e.g., environmental exposures, injury, infection) that can explain the member’s symptoms or medical condition; AND

f. Multigene panel testing is more practical testing to diagnose the member’s condition than the separate single gene tests or targeted panels that would be recommended (with supporting documentation provided); AND

g. Clinical presentation of the member’s condition does not fit a well-described syndrome for which single-gene or targeted panel testing is available (e.g., comparative genomic hybridization/chromosomal microarray analysis) or single-gene or targeted panel testing is not clinically appropriate for the member’s condition (with supporting clinical documentation provided).

The Plan considers the multigene panel testing to be medically necessary only when ALL of the criteria outlined above (in items a through g) are met; disease-targeted genetic testing is considered medically necessary as an alternative when Plan criteria are met in the Medical Policy Statement section (and according to guidelines specified in the Limitations section of this policy). See the Genetic Testing Guidelines and Pharmacogenetics policy, policy number OCA 3.727, for guidelines related to multigene panel testing to determine response to drug metabolism and adjuvant therapy and the use of multigene panels to determine hereditary cancer susceptibility for other types of cancer.

See the Plan’s policy, Experimental and Investigational Treatment (policy number OCA 3.12), for the product-specific definitions of experimental or investigational treatment. Review Plan policy, Medically Necessary (policy number OCA 3.14), for the product-specific definitions of medically necessary treatment. Review Plan policy, Genetic Testing Guidelines and Pharmacogenetics, policy number OCA 3.727, for genetic testing guidelines that are not be included in this Plan policy, including indications for whole exome sequencing, whole genome sequencing, and other molecular, chromosomal, and biochemical genetic testing.

Definitions

**Antiphospholipid Antibody Screening:** Testing for antiphospholipid antibody syndrome, a condition in which the plasma levels of antibodies (including lupus anticoagulant, cardiolipin antibodies, or other antibodies against phospholipids) are elevated, adversely affecting coagulation processes in the bloodstream. Antiphospholipid antibody syndrome is a cause of acquired thrombophilia.

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Antiprothrombin III Deficiency: Antiprothrombin III is a nonvitamin K-dependent protease that inhibits coagulation by lysing thrombin and factor Xa. Congenital antithrombin III deficiency is an autosomal dominant disorder in which an individual inherits at least one copy of a defective gene, leading to increased risk of venous and arterial thrombosis.

Factor V Leiden (FVL) Gene Mutation (p.Arg506Gln): Factor V Leiden results from a point mutation that causes an amino acid change at position 506 in factor V and is a common genetic defect related to hereditary (inherited) thrombophilia.

First-Degree Relative: A blood relative of an individual who shares approximately 50% of their genes defined as a parent, full sibling, and children.

Genetic Testing: According to U.S. Library of Medicine, genetic testing is defined as a type of medical test that identifies changes in chromosomes, genes, or proteins. The results of a genetic test can confirm or rule out a suspected genetic condition or help determine a person’s chance of developing or passing on a genetic disorder. More than 1,000 genetic tests are currently in use, and more are being developed. Several methods can be used for genetic testing:

1. Molecular genetic tests (or gene tests) study single genes or short lengths of DNA to identify variations or mutations that lead to a genetic disorder.

2. Chromosomal genetic tests analyze whole chromosomes to see if there are large genetic changes, such as an extra copy of a chromosome or missing DNA, that cause a genetic condition.

3. Biochemical genetic tests study the amount or activity level of proteins; abnormalities in either can indicate changes to the DNA that result in a genetic disorder.

Multigene Panel Tests: Tests that evaluate more than one (1) gene simultaneously to detect changes in gene expression most commonly associated with certain diseases and other genes that may have limited evidence of an association to the disorder. Multigene panel tests may involve traditional exon-by-exon sequencing of targeted genes to identify genetic variants or use next-generation sequencing. Each laboratory establishes its own set of criteria for selecting the genes represented in a panel, even when panels are used for the same or similar clinical indications. The lack of regulatory oversight of genetic testing means that laboratories can change the components of a panel at any time, making it difficult to evaluate the clinical utility of multigene panel tests.

Next-Generation Sequencing (NGS or Massively Parallel Sequencing): Genetic testing that involves sequencing of millions of DNA fragments using the following three (3) levels of molecular analysis: (1) Disease-targeted gene panels to sequence genes with an established role in the targeted disease, (2) exome sequencing of coding regions of the genome to include less common variants associated with the disease (i.e., a coding region is the segment of a gene that contains a protein-coding sequence...
called an exon in all 22,000 genes of the human genome); and (3) genome sequencing of both the coding and non-coding regions of the genome (i.e., the non-coding regions in between exons are called introns). Multiple sequencing platforms and different processes result in variability in test results among laboratories.

**Protein C Deficiency:** Protein C is a vitamin K-dependent protein synthesized in the liver. The gene for protein C is located on chromosome 2 (2q13-14) and appears to be closely related to the gene for factor IX. A deficiency in protein C predisposes an individual to thrombophilia.

**Protein S Deficiency:** Protein S is a vitamin K-dependent glycoprotein, is a cofactor of the protein C system. In the presence of protein S, activated protein C directly inhibits prothrombin activation via interactions with other coagulation factors. Two homologous genes for protein S (gene PROS1 and PROS2) map to chromosome 3. A deficiency in protein S predisposes an individual to thrombophilia.

**Prothrombin Gene G20210A Mutation:** A mutation in the human prothrombin gene and is a common genetic defect related to hereditary (inherited) thrombophilia. Prothrombin (factor II) is a vitamin K-dependent protein which is the precursor of thrombin, the end-product of the coagulation cascade.

**Thrombophilia:** Hereditary conditions that are risk factors for venous thrombosis.

**Whole Exome Sequencing (WES)/Whole Genome Sequencing (WGS):** WES captures and sequences at a deep level the protein coding regions (called exons) of an individual’s genes using first-generation sequencing techniques or next-generation sequencing to detect disease-causing variants and discover gene targets. While exons represent only 1% of the genome, they account for approximately 85% of disease-causing variants. Through identification of variants across the exome, WES avoids the need to run multiple single-gene tests, which require prior information about variants affecting the disease. WES has been performed in a number of cancers, whereby comparison between tumor DNA and normal DNA from the same individual allows identification of variants specific to the tumor, which may provide information used for diagnosis and treatment. WES is targeted sequencing of the subset of the human genome that contains functionally important sequences of protein-coding DNA, while whole genome sequencing (WGS) uses next-generation sequencing techniques to sequence both coding and non-coding regions of the genome. Because WES only evaluates the protein-coding regions of the human genome (exoms), WES is a more cost-effective alternative to WGS. WES produces a smaller, more manageable data set with faster turnaround time for analyses than WGS. WGS has the ability to detect structural variations located outside of the exome that may be related to many diseases and cannot be identified with WES. WES and WGS have been proposed to be more efficient than traditional sequencing methods in discovering the genetic causes of diseases, but there remain issues of error rates due to technical challenges and difficulty interpreting potential causative variants from variants of unknown significance generated for each patient. Examples of tests include but are not limited to the following: TruGenome tests (Illumina), Endometrial Cancer Panel (GeneDx), ExomeNext and ExomeNext-Rapid (Ambry Genetics), XomeDx™ test (GeneDx), mtSEEK Whole Mitochondrial Genome Analysis (Courtagen Life Sciences Inc.), and/or nucSEEK Comprehensive Sequence Analysis of Nuclear Mitochondrial Exome (Courtagen Life Sciences, Inc.). According to The American College of

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Obstetricians and Gynecologists (Committee Opinion Number 682), the routine use of whole genome or whole exome sequencing for prenatal diagnosis is not recommended outside of the context of clinical trials until sufficient peer-reviewed data and validation studies are published. See the Genetic Testing Guidelines and Pharmacogenetics medical policy (policy number OCA 3.727) rather than this policy for Plan guidelines related to WES and WGS.

### Applicable Coding

The Plan uses and adopts up-to-date Current Procedural Terminology (CPT) codes from the American Medical Association (AMA), International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) diagnosis codes developed by the World Health Organization and adapted in the United Stated by the National Center for Health Statistics (NCHS) of the Centers for Disease Control under the U.S. Department of Health and Human Services, and the Health Care Common Procedure Coding System (HCPCS) established and maintained by the Centers for Medicare & Medicaid Services (CMS). Because the AMA, NCHS, and CMS may update codes more frequently or at different intervals than Plan policy updates, the list of applicable codes included in this Plan policy is for informational purposes only, may not be all inclusive, and is subject to change without prior notification. Whether a code is listed in the Applicable Coding section of this Plan policy does not constitute or imply member coverage or provider reimbursement. Providers are responsible for reporting all services using the most up-to-date industry-standard procedure and diagnosis codes as published by the AMA, NCHS, and CMS at the time of the service.

Providers are responsible for obtaining prior authorization for the services specified in the Medical Policy Statement section and Limitation section of this Plan policy, even if an applicable code appropriately describing the service that is the subject of this Plan policy is not included in the Applicable Coding section of this Plan policy. Coverage for services is subject to benefit eligibility under the member’s benefit plan. Please refer to the member’s benefits document in effect at the time of the service to determine coverage or non-coverage as it applies to an individual member. See Plan reimbursement policies for Plan billing guidelines.

Refer to the Medical Policies page of the Provider folder at [www.bmchp.org](http://www.bmchp.org) (for BMC HealthNet Plan members, including Senior Care Options members) or [www.wellsense.org](http://www.wellsense.org) (for Well Sense Health Plan members) for information about additional, condition-specific genetic testing and gene expression profiling policies. Plan prior authorization is required for all genetic testing, even when the applicable code for the genetic test is not listed in a Plan policy.

### CPT Codes

<table>
<thead>
<tr>
<th>CPT Codes</th>
<th>Description: Codes Covered When Medically Necessary</th>
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<tbody>
<tr>
<td>81240</td>
<td>F2 (prothrombin, coagulation factor II) (e.g., hereditary hypercoagulability) gene analysis, 20210G&gt;A variant</td>
</tr>
<tr>
<td>81241</td>
<td>F5 (coagulation factor V) (e.g., hereditary hypercoagulability) gene analysis, Leiden variant</td>
</tr>
</tbody>
</table>

Genetic Testing for Hereditary Thrombophilia

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<table>
<thead>
<tr>
<th>CPT Codes</th>
<th>Description: Codes Considered Not Medically Necessary for Thrombophilia Testing</th>
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<tbody>
<tr>
<td>81291</td>
<td>MTHFR (5,10-methylenetetrahydrofolate reductase) (e.g., hereditary hypercoagulability) gene analysis, common variants (e.g., 677T, 1298C)</td>
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<tr>
<td></td>
<td>Plan note: MTHFR gene analysis is considered experimental and investigational to determine thrombophilia. See Plan policy, Genetic Testing Guidelines and Pharmacogenetics, policy number OCA 3.727, for prior authorization guidelines for MTHFR genetic testing for other indications.</td>
</tr>
<tr>
<td>81400</td>
<td>Molecular pathology procedure, Level 1 (e.g., identification of single germline variant [e.g., SNP] by techniques such as restriction enzyme digestion or melt curve analysis)</td>
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<tr>
<td></td>
<td>F5 (coagulation factor V) (e.g., hereditary hypercoagulability), HR2 variant</td>
</tr>
<tr>
<td></td>
<td>Plan note: This CPT code includes numerous types of tests, including F5 HR2 variant analysis. Factor V HR2 haplotype (F5 HR2) variant testing is considered experimental and investigational to determine thrombophilia, including reflex testing of F5 HR2 following identification of member with the F5 p.Arg506Gln (FVL) variant. See Plan policy, Genetic Testing Guidelines and Pharmacogenetics, policy number OCA 3.727, for prior authorization guidelines for additional tests included in this CPT code.</td>
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**Clinical Background Information**

Hypercoagulability, or thrombophilia, leads to the inappropriate formation of blood clots, and most commonly manifests as venous thromboembolism (VTE), such as deep vein thrombosis (DVT) in the legs, pulmonary embolism (PE), or in women (including individuals born with female reproductive organs and/or with typical female karyotype with two [2] X chromosomes), as adverse pregnancy outcomes. VTE affects approximately 300,000 to 600,000 individuals each year in the United States; the annual incidence of first-time VTE is approximately 1 per 1000 individuals. Typical precipitating factors for VTE include major trauma, recent surgery, immobilization, high body mass index (BMI), fractures, medical illness, or aging. Among women (including individuals born with female reproductive organs and/or with typical female karyotype with two [2] X chromosomes), risk is increased during pregnancy and use of oral contraceptives or hormone replacement therapy (HRT). Once diagnosed, treatment options include initial short-term anticoagulation that may be extended (e.g., lifetime therapy) based on risk of recurrence balanced with risk of major hemorrhage. Heritable genetic factors also contribute to the risk of VTE.

Inherited thrombophilias include the following abnormalities: Activated protein C resistance (factor V Leiden mutations), protein C deficiency, protein S deficiency, prothrombin deficiency, and prothrombin gene mutation. The most common type of inherited thrombophilia is a factor V Leiden (FVL) mutation (F5 gene variant p.Arg506Gln), which accounts for up to 50% of the inherited thrombophilia.

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syndromes; deficiencies in protein S, protein C, and antithrombin account for most of the remaining cases.

A key part of the clotting mechanism in the factor V protein is the activation of prothrombin to thrombin, which is required for the conversion of soluble fibrinogen to insoluble fibrin. A common sequence variant of the prothrombin gene, G20210A (c.*96G>A), is associated with elevated plasma prothrombin levels, which is also a risk factor for VTE. The discovery of FVL and prothrombin G20210A as primary causes of familial thrombosis has remarkably influenced genetic testing among patients with VTE or recurrent obstetric complications.

Genetic predisposition to hyperhomocysteinemia, which is associated with vascular disease and VTE, may be caused by the C677T (c.677C>T) sequence variant of the methylenetetrahydrofolate reductase (MTHFR) gene located on chromosome 1 at band p36. There is insufficient published scientific evidence to support the clinical utility of MTHFR genetic testing to diagnose thrombophilia.

A group of gene variants linked to factor V Leiden, collectively known as the HR2 haplotype (Factor V HR2), has been studied for its possible association with thrombophilia, alone and in conjunction with p.Arg506Gln (FVL) gene variant. There is insufficient scientific evidence at this time to support factor V (F5) HR2 haplotype testing to identify hypercoagulability.

Genetic susceptibility may help explain VTE in general; however, it is important to note that many individuals who carry a genetic variant associated with thrombosis may never develop thrombotic event(s) even in the presence of an obvious precipitating factor. At the current time, there is insufficient scientific evidence in the peer reviewed medical literature to support the effectiveness of genetic testing for thrombophilia to treat individuals taking oral contraceptives, asymptomatic individuals, or individuals with first VTE with no family history remain unproven. Additional studies are needed to establish the clinical benefits on health outcomes for these indications.

The Food and Drug Administration (FDA) only regulates genetic tests sold as kits and has practiced enforcement discretion for laboratory-developed tests (LDTs), which represent the majority of genetic tests marketed in the United States. While the Centers of Medicare & Medicaid Services (CMS) does regulation the clinical laboratories in which LDTs are performed, CMS does not evaluate whether the genetic tests are clinically meaningful.

At the time of the Plan’s most recent policy review, the Centers for Medicare & Medicaid Services (CMS) has implemented the following national coverage determinations (NCDs) related to genetic tests: NCD for Colorectal Cancer Screening Tests (210.3) for coverage of immunoassay and guaiac fecal occult blood tests and the Cologuard™ - Multitarget Stool DNA (sDNA) test when CMS applicable criteria are met, NCD for Pharmacogenomic Testing for Warfarin Response (90.1) for medically necessary indications for testing as determined by CMS, and NCD for Cytogenetic Studies (190.3) for coverage based on CMS guidelines. Medicare uses a combination of national and local coverage determinations for making coverage decisions for genetic tests. Medicare administrative contractors (MAC) may implement local coverage determinations (LCDs) that apply only within their own
Genetic Testing for Hereditary Thrombophilia

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Centers for Medicare & Medicaid Services (CMS). National Coverage Determination (NCD) for Colorectal Cancer Screening Tests (210.3). Effective Date October 9, 2014. Implementation Date September 8, 2015. Accessed at: https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCId=281&ncdver=5&CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=Massachusetts&KeyWord=colorectal+cancer&KeyWordLookUp=Title&KeyWordSearchType=And&bc=gA

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Centers for Medicare & Medicaid Services (CMS). National Coverage Determination (NCD) for Cytogenetic Studies (190.3). July 16, 1998. Accessed at: https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=198&ncdver=1&CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=Massachusetts&KeyWord=cytogenetic&KeyWordLookUp=Title&KeyWordSearchType=And&lcd_id=24308&lcd_version=26&basket=lcd*3a%2424308*3a%2426*3a%24Genetic+Testing*3a%24MAC+-+Part+B*3a%24Noridian+Administrative+Services%257C%257C+LLC+(03102)*3a%24&bc=gAAAAACAAA

Centers for Medicare & Medicaid Services (CMS). National Coverage Determination (NCD) for Pharmacogenomic Testing for Warfarin Response (90.1). August 3, 2009. Accessed at: https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=333&ncdver=1&CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=Massachusetts&KeyWord=warfarin&KeyWordLookUp=Title&KeyWordSearchType=And&lcd_id=24308&lcd_version=26&basket=lcd*3a%2424308*3a%2426*3a%24Genetic+Testing*3a%24MAC+-+Part+B*3a%24Noridian+Administrative+Services%257C%257C+LLC+(03102)*3a%24&bc=gAAAAACAAA


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Genetic Testing for Hereditary Thrombophilia

16 of 23


Genetic Testing for Hereditary Thrombophilia

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<table>
<thead>
<tr>
<th>Original Approval Date</th>
<th>Original Effective Date* and Version Number</th>
<th>Policy Owner</th>
<th>Approved by</th>
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<tr>
<td>Regulatory Approval: N/A</td>
<td>03/01/14 Version 1</td>
<td>Medical Policy Manager as Chair of Medical Policy, Criteria, and Technology Assessment Committee (MPCTAC) and member of Quality Improvement Committee (QIC)</td>
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<td>Internal Approval: 11/20/13: MPCTAC 12/03/13: MPCTAC (electronic vote) 12/19/13: QIC</td>
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*Effective Date for the Senior Care Options Product(s): 01/01/16

Policy Revisions History

<table>
<thead>
<tr>
<th>Review Date</th>
<th>Summary of Revisions</th>
<th>Revision Effective Date and Version Number</th>
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<tr>
<td>11/01/14</td>
<td>Review for effective date 03/01/15. Revised criteria in the Medical Policy</td>
<td>03/0/15 Version 2</td>
<td>11/19/14: MPCTAC 12/10/14: QIC</td>
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### Policy Revisions History

<table>
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<th>Date</th>
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<tr>
<td>11/01/15</td>
<td>Review for effective date 01/01/16. Updated Summary, Definitions, and References sections. Changed review calendar.</td>
<td>01/01/16</td>
<td>11/18/15: MPCTAC 11/25/15: MPCTAC (electronic vote) 12/09/15: QIC</td>
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<td>01/01/16</td>
<td>Review for effective date 05/01/16. Updated Description of Item or Service, Definitions, Clinical Background Information, and References sections. Revised criteria in the Limitations section.</td>
<td>05/01/16</td>
<td>01/20/16: MPCTAC 02/10/16: QIC</td>
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<td>09/28/16</td>
<td>Review for effective date 11/01/16. Administrative changes to clarify language related to gender.</td>
<td>11/01/16</td>
<td>09/30/16: MPCTAC (electronic vote) 10/12/16: QIC</td>
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<td>01/01/17</td>
<td>Review for effective date 05/01/17. Updated Summary, Definitions, Clinical Background Information, References, and References to Applicable Laws and Regulations sections. Revised criteria in the Medical Policy Statement and Limitations sections.</td>
<td>05/01/17</td>
<td>01/18/17: MPCTAC 02/08/17: QIC</td>
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### Last Review Date

01/01/17

### Next Review Date

01/01/18

### Authorizing Entity

QIC

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Other Applicable Policies

Medical Policy - Chromosomal Microarray Analysis for Unexplained Intellectual Disabilities and/or Multiple Congenital Anomalies, policy number OCA 3573
Medical Policy - Experimental and Investigational Treatment, policy number OCA 3.12
Medical Policy - Gene Expression Profiling of Tumor Tissue to Predict Cancer Recurrence and Risk Stratification (Including Oncotype DX™ and Other Tests), policy number OCA 3.572
Medical Policy - Genetic Testing for Familial Malignant Melanoma, policy number OCA 3.78
Medical Policy - Genetic Testing for Fragile X-Associated Disorders, policy number OCA 3.571
Medical Policy - Genetic Testing Guidelines and Pharmacogenetics, policy number OCA 3.727
Medical Policy - Genetic Testing for Hereditary Breast and Ovarian Cancer Syndrome, policy number OCA 3.57
Medical Policy - Genetic Testing for Hereditary Colorectal Cancer, policy number OCA 3.64
Medical Policy - Medically Necessary, policy number OCA 3.14
Medical Policy - Preimplantation Genetic Testing (Preimplantation Genetic Diagnosis and Pregenetic Screening), policy number OCA 3.726

Reference to Applicable Laws and Regulations


Massachusetts General Law. Chapter 111. Section 70G. (M.G.L. c. 111 sec. 70G.) Genetic information and reports protected as private information; prior written consent for genetic testing. Accessed at: https://malegislature.gov/Laws/Generallaws/PartI/TitleXVI/Chapter111/Section70G

Disclaimer Information: *

Medical Policies are the Plan’s guidelines for determining the medical necessity of certain services or supplies for purposes of determining coverage. These Policies may also describe when a service or supply is considered experimental or investigational, or cosmetic. In making coverage decisions, the Plan uses these guidelines and other Plan Policies, as well as the Member’s benefit document, and when appropriate, coordinates with the Member’s health care Providers to consider the individual Member’s health care needs.

Plan Policies are developed in accordance with applicable state and federal laws and regulations, and accrediting organization standards (including NCQA). Medical Policies are also developed, as appropriate, with consideration of the medical necessity definitions in various Plan products, review of current literature, consultation with practicing Providers in the Plan’s service area who are medical experts in the particular field, and adherence to FDA and other government agency policies. Applicable state or federal mandates, as well as the Member’s benefit document, take precedence over these guidelines. Policies are reviewed and updated on an annual basis, or more frequently as needed. Treating providers are solely responsible for the medical advice and treatment of Members.

The use of this Policy is neither a guarantee of payment nor a final prediction of how a specific claim(s) will be adjudicated. Reimbursement is based on many factors, including member eligibility and benefits on the date of service; medical necessity; utilization management guidelines (when applicable); coordination of benefits; adherence with applicable Plan policies and procedures; clinical coding criteria; claim editing logic; and the applicable Plan – Provider agreement.

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