MP 2.04.582
Genetic Testing for Inherited Thrombophilia

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Section: Medicine

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POLICY

Genetic testing for Factor V and Factor II Blood Clotting Protein mutations may be considered medically necessary for any of the following conditions:

- Age less than 50, any venous thrombosis; or
- Myocardial infarction in female smokers under age of 50; or
- Recurrent venous thrombosis; or
- First or second degree relative of individuals with venous thrombosis under age of 50; or
- Relative with confirmed Factor V or Factor II mutation; or
- Venous thrombosis and a first or second degree relative with venous thrombosis; or
- Venous thrombosis in pregnant women or women taking oral contraceptives; or
- Venous thrombosis in unusual sites (such as hepatic, mesenteric and cerebral veins).

Genetic testing for Factor V and Factor II mutations is considered investigational for all other indications.

Factor V HR2 allele DNA mutation analysis is considered investigational.

Other genetic tests for inherited thrombophilia, including MTHFR are considered investigational.

The following tests are considered investigational in the evaluation of recurrent pregnancy loss:

- Tests for inherited thrombophilic disorders:
  - antithrombin III antibody;
  - antithrombin III antigen;
  - factor V Leiden (genetic testing);
  - factor V Leiden coagulation (ACPR);
  - prothrombin G20210A mutation;
  - serum homocysteine;
  - protein C activity;
  - protein C antigen;
  - protein S activity;
  - protein S antigen;
The American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from ACMG, AMP, and the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “variant of uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td></td>
<td>variant</td>
<td></td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
</tr>
<tr>
<td></td>
<td>variant</td>
<td></td>
</tr>
</tbody>
</table>

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

GENETIC COUNSELING

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual’s family. Genetic counseling may alter the utilization of genetic testing substantially and may
reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

CODING

81240: F2 (prothrombin, coagulation factor II) (e.g., hereditary hypercoagulability) gene analysis, 20210G>A variant

81241: F5 (coagulation Factor V) (e.g., hereditary hypercoagulability) gene analysis, Leiden variant

81291: MTHFR (5, 10-methylenetetrahydrofolate reductase) (e.g., hereditary hypercoagulability) gene analysis, common variants (e.g., 677T, 1298C).

The genes above are also found in panel test: 81400 Pathology testing Level 1.

BENEFIT APPLICATION

BLUECARD/NATIONAL ACCOUNT ISSUES

Some plans may have contract or benefit exclusions for genetic testing.

BACKGROUND

VENOUS THROMBOEMBOLISM

The overall U.S. incidence of venous thromboembolism (VTE) is approximately 1 per 1000 person-years, and the lifetime clinical prevalence is approximately 5%, accounting for 100,000 deaths annually.1 Risk is strongly age-related, with the greatest risk in older populations. VTE also recurs frequently; estimated cumulative incidence of first VTE recurrence is 30% at 10 years.1 These figures do not separate patients with known predisposing conditions from those without.

Risk factors for thrombosis include a variety of clinical and demographic variables, and at least 1 risk factor can be identified in approximately 80% of patients with thrombosis. The following list includes the most important risk factors:

- Malignancy
- Immobility
- Surgery
- Obesity
- Pregnancy
- Hormonal therapy such as estrogen/progestin or selective estrogen modulator products
- Systemic lupus erythematosus and/or other rheumatologic disorders
- Myeloproliferative disorders
- Liver dysfunction
- Nephrotic syndrome
- Hereditary factors

Pregnancy often is considered a special circumstance because of its frequency and unique considerations of preventing and treating VTE. Pregnancy is associated with a 5- to 10-fold increase in VTE risk, and absolute VTE risk in pregnancy is estimated to be 1 to 2 per 1000 deliveries.2 In women with a history of pregnancy-related VTE, risk of recurrent VTE with subsequent pregnancies is increased greatly at approximately 100-fold.2

Treatment

Treatment of thrombosis involves anticoagulation for a minimum of 3 to 6 months. After this initial treatment period, patients deemed to be at a continued high risk for recurrent thrombosis may continue
on anticoagulation therapy for longer periods, sometimes indefinitely. Anticoagulation is effective for reducing subsequent risk of thrombosis but carries its own risk of bleeding.

INHERITED THROMBOPHILIA

Inherited thrombophilias are a group of clinical conditions characterized by genetic variant defects associated with a change in the amount or function of a protein in the coagulation system and a predisposition to thrombosis. Not all individuals with a genetic predisposition to thrombosis will develop VTE. The presence of inherited thrombophilia will presumably interact with other VTE risk factors to determine an individual’s VTE risk.

A number of conditions fall under the classification of inherited thrombophilias. Inherited thrombophilias include the following conditions, which are defined by defects in the coagulation cascade:

- Activated protein C resistance (factor V Leiden [FVL] variant)
- Prothrombin (factor II) gene variant (G20210A)
- Protein C deficiency
- Protein S deficiency
- Prothrombin deficiency
- Hyper-homocysteinemia (5,10-methylenetetrahydrofolate reductase [MTHFR] variant).

The most common type of inherited thrombophilia is FVL, which accounts for up to 50% of inherited thrombophilia syndromes. In unselected patients with an idiopathic thrombosis, the incidence of FVL is 17% to 24%, compared with a rate of 5% to 6% in normal controls. The prothrombin G20210A variant is found less commonly, in approximately 5% to 8% of unselected patients who have thrombosis compared with 2% to 2.5% of normal controls.

GENETIC TESTING

Genetic testing for gene variants associated with thrombophilias is available for FVL, the prothrombin G20210A variant, and MTHFR. Genetic testing for inherited thrombophilia can be considered in several clinical situations. Clinical situations addressed herein include the following:

- Assessment of thrombosis risk in asymptomatic patients (screening for inherited thrombophilia)
- Evaluation of a patient with established thrombosis, for consideration of change in anticoagulant management based on results
- Evaluation of close relatives of patients with documented inherited thrombophilia or with a clinical and family history consistent with an inherited thrombophilia
- Evaluation of patients in other situations who are considered at high risk for thrombosis (e.g., pregnancy, planned major surgery, exogenous hormone use)

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Commercial thrombophilia genetic tests are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

Several genetic tests for thrombophilia have been cleared for marketing by FDA through the 510(k) process for use as an aid in the diagnosis of patients with suspected thrombophilia. Some of these tests are listed in Table 1.
Table 1. Genetic Tests for Thrombophilia Cleared by FDA

<table>
<thead>
<tr>
<th>Test</th>
<th>Manufacturer</th>
<th>Location</th>
<th>Date Cleared</th>
<th>510(k) No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMPACT Dx™ Factor V Leiden and Factor II Genotyping Test</td>
<td>Agena Biosciencea</td>
<td>San Diego, CA</td>
<td>06/14</td>
<td>K132978</td>
</tr>
<tr>
<td>Invader® Factor II, V, and MTHFR (677, 1298) tests</td>
<td>Hologic</td>
<td>Marlborough, MA</td>
<td>04-06/11</td>
<td>K100943, K100980, K100987, K100496</td>
</tr>
<tr>
<td>VeraCode® Genotyping Test for Factor V and Factor II</td>
<td>Illumina</td>
<td>San Diego, CA</td>
<td>04/28/10</td>
<td>K093129</td>
</tr>
<tr>
<td>eSensor® Thrombophilia Risk Test, FII-FV, FII, FV and MTHFR (677, 1298) Genotyping Tests</td>
<td>GenMark Dxb</td>
<td>Carlsbad, CA</td>
<td>04/22/10</td>
<td>K093974</td>
</tr>
<tr>
<td>INFINITI™ System Assay for Factor II &amp; Factor V</td>
<td>AutoGenomics</td>
<td>Carlsbad, CA</td>
<td>02/07/07</td>
<td>K060564</td>
</tr>
<tr>
<td>Xpert® Factor II and Factor V Genotyping Assay</td>
<td>Cepheid</td>
<td>Sunnyvale, CA</td>
<td>09/18/09</td>
<td>K082118</td>
</tr>
<tr>
<td>Verigene® Factor F2, F5, and MTHFR Nucleic Acid Test</td>
<td>Nanosphere</td>
<td>Northbrook, IL</td>
<td>10/11/07</td>
<td>K070597</td>
</tr>
<tr>
<td>Factor V Leiden Kit</td>
<td>Roche Diagnostics</td>
<td>Indianapolis, IN</td>
<td>12/17/03</td>
<td>K033607</td>
</tr>
<tr>
<td>Factor II (Prothrombin) G20210A Kit</td>
<td>Roche Diagnostics</td>
<td>Indianapolis, IN</td>
<td>12/20/03</td>
<td>K033612</td>
</tr>
</tbody>
</table>

FDA: Food and Drug Administration.
a FDA marketing clearance was granted to Sequenom Bioscience before it was acquired by Agena.
b FDA marketing clearance was granted to Osmetech Molecular Diagnostics.

Other commercial laboratories may offer a variety of functional assays and genotyping tests for F2 (prothrombin, coagulation factor II) and F5 (coagulation factor V), and single or combined genotyping tests for 5,10-methylenetetrahydrofolate reductase (MTHFR).

On April 6, 2017, FDA permitted marketing of 23andMe Personal Genome Service Genetic Health Risk (GHR) tests for 10 diseases or conditions. These direct-to-consumer tests are the first authorized by FDA that provide information on an individual’s genetic predisposition to certain medical diseases or conditions, which may help to make decisions about lifestyle choices or to inform discussions with a health care professional. The 23andMe GHR tests work by isolating DNA from a saliva sample, which is then tested for more than 500,000 genetic variants. The presence or absence of some of these variants is associated with an increased risk for developing any 1 of 10 diseases or conditions. Testing for hereditary thrombophilia (2 variants in the F5 and F2 genes; relevant for European descent) is included.
RATIONALE

This evidence review was originally created in July 2012 and have been updated regularly with searches of the MEDLINE database. The most recent literature review was performed through March 5, 2018 (see Appendix Table 1 for genetic testing categories).

Validation of the clinical use of any genetic test focuses on 3 main principles: (1) analytic validity, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent; (2) clinical validity, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and (3) clinical utility (i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes). The following is a summary of the key literature.

MTHFR VARIANT TESTING

Variants in the 5,10-methylenetetrahydrofolate reductase (MTHFR) gene are associated with hyperhomocysteinemia, which in turn is considered a weak risk factor for venous thromboembolism (VTE). However, clinical utility of testing for homocysteine levels has not been established. There is a large body of literature on the association of homocysteine levels with coronary artery disease, and clinical trials have assessed the impact of lowering homocysteine levels. This body of evidence has indicated that testing or treating for homocysteinemia is not associated with improved outcomes.

The evidence for the association between MTHFR and VTE is not definitive. Some studies have shown an association, while others have not. One larger study (N=9231), the 2007 MEGA study, showed no association between the MTHFR 677C>T variant with recurrent VTE. A 2007 randomized controlled trial (RCT) reported no reduction in VTE associated with treatment of hyperhomocysteinemia.

Section Summary: MTHFR Variant Testing

Published evidence on the utility of testing for MTHFR variants in patients who have or are at risk for VTE is limited. Given the available evidence, and lack of clinical utility for serum homocysteine testing in general, it is unlikely that testing for MTHFR will improve outcomes.

FACTOR V LEIDEN AND PROTHROMBIN VARIANT TESTING

Analytic Validity

Analytic validity refers to the accuracy of detecting a specific variant when it is present and excluding it when absent.

For a 2009 evidence review prepared for the Agency for Healthcare Research and Quality (AHRQ), researchers performed a comprehensive evaluation of analytic validity studies. Forty-one studies compared genetic testing for factor V Leiden (FVL) with a reference standard. Concordance between the tests was high, ranging from 93% to 100%, and was 100% in most studies. This AHRQ report also reviewed 23 studies on the concordance of prothrombin gene variants with a reference standard and found that nearly all studies reported a 100% concordance. Twelve studies reported multiplex methods to test simultaneously for both FVL and the prothrombin G20210A variant, all of which reported 100% concordance with reference standards.

Bradley et al (2012) reviewed the analytic validity of FVL and prothrombin variant testing in pregnancy as reported in individual studies and meta-analyses. For studies performed in the United States, the combined analytic sensitivity and specificity for FVL testing exceeded 99%. For the prothrombin G20210A variant, the analytic sensitivity was 98.4% and the analytic specificity was 99.7%.
Subsection Summary: Analytic Validity

The analytic validity of genetic testing for inherited thrombophilia is high. The analytic sensitivity and specificity for FVL testing both exceed 99%, and the analytic sensitivity and specificity for the prothrombin G20210A variant both exceed 98%.

Clinical Validity

Clinical validity (and clinical utility) will be discussed for 4 distinct patient populations. They are:

- Individuals without a personal history of VTE
- Individuals with a personal history of VTE
- Family members of individuals with thrombophilia
- Pregnancy and other high-risk situations.

The clinical validity of testing for inherited thrombophilias is best determined by the predictive ability of the test for future thromboembolic events, both in patients with and without prior VTE. Highest quality evidence for this question comprises prospective cohort studies in which patients with and without the variant are followed for development of VTE. A few studies are prospective, nested within RCTs, in which patients with and without variants are compared.

Individuals without a Personal History of VTE

Individuals with FVL or prothrombin variants have an elevated risk of thrombosis compared with the general population. For individuals with the FVL variant, the risk may be 2- to 5-fold higher than that in the general population. In 1 retrospective study (1998) of first-degree relatives of individuals with documented VTE and heterozygosity for FVL, those with an FVL variant had an absolute annual risk for a first VTE episode of 0.45%, compared with an annual incidence of 0.1% in those family members without the variant.  

For the prothrombin G20210A variant, risk also has been estimated to be 2 to 5 times greater than the general population. In a 2009 meta-analysis of 79 studies, combined relative risk was 3.0. Heterozygosity for the prothrombin G20210A variant also is associated with an increased risk of upper-extremity thrombosis, estimated to be 5 times that of the general population.

Individuals with a Personal History of VTE

Factor V Leiden

The 2009 AHRQ report reviewed the evidence on recurrence risk for patients with a history of VTE and the FVL variant. For individuals with a heterozygous FVL variant, 13 studies compared recurrence risk to a variant with recurrence risk without a variant. Pooled analysis of these 13 studies yielded an odds ratio (OR) of 1.56 (95% confidence interval [CI], 1.14 to 2.12) for recurrent VTE in patients with the FVL variant. For patients with a homozygous variant, 7 studies evaluated recurrence risk. Pooled odds ratio for recurrent VTE in these studies was 2.65 (95% CI, 1.18 to 5.97).

Not all studies have reported an increased risk of recurrent VTE in patients with inherited thrombophilia. For example, the 2005 Leiden Thrombophilia Study (LETS) followed 474 patients who had completed a course of anticoagulation for a mean of 7.3 years. All patients were tested for thrombophilia at baseline, with 20% found to have an FVL variant and 6% a prothrombin variant. Recurrence did not increase either for patients with a FVL variant or for patients with a prothrombin variant. For FVL, there was a mild increase in recurrence risk that was not statistically significant on multivariate analysis (hazard ratio [HR], 1.3; 95% CI, 0.8 to 2.1). For the prothrombin G20210A variant, there was no increased risk of recurrence (HR=0.7; 95% CI, 0.3 to 2.0). Factors that predicted recurrence were mainly clinical variables, such as provoked versus unprovoked VTE, patient sex, and oral contraceptive use.
A larger RCT included in the AHRQ review was the 2008 ELATE trial, which randomized 738 patients from 16 clinical centers to low-intensity versus conventional-intensity anticoagulation.\textsuperscript{19} All patients were tested for inherited thrombophilias, and recurrence risk was calculated for patients with and without inherited thrombophilia. For patients with an FVL variant, there was no increased risk of recurrence over a mean follow-up of 2.3 years (HR=0.7; 95% CI, 0.2 to 2.6).

**Prothrombin G20210A Variant**

The 2009 AHRQ evidence report identified 18 studies that evaluated recurrence risk in patients heterozygous for the prothrombin G20210A variant. Some of these studies included only heterozygotes, and others combined both heterozygotes and homozygotes. For 9 studies that included only heterozygotes, pooled odds ratio for recurrent VTE was 1.45 (95% CI, 0.96 to 2.2). For 7 studies that did not specify homozygous or heterozygous, the combined odds ratio was 0.73 (95% CI, 0.37 to 1.44).

The prothrombin G20210A variant is less common and, therefore, the number of patients evaluated in clinical trials and cohort studies is smaller than for FVL. In the ELATE trial, risk of recurrent VTE in those with the prothrombin G20210A variant could not be calculated because there were no recurrences among 60 patients with the variant.\textsuperscript{19} In the LETS study, 29 patients had a prothrombin variant.\textsuperscript{18} For patients with a prothrombin variant, there was no increased risk of recurrence (HR=0.7; 95% CI, 0.3 to 2.0). Factors that predicted recurrence were mainly clinical variables, such as provoked versus unprovoked VTE, patient sex, and oral contraceptive use.

**Family Members of Individuals With Thrombophilia**

**Factor V Leiden**

The 2009 AHRQ report identified 9 studies that evaluated VTE risk in family members of a proband with a heterozygous variant. The pooled odds ratio for future VTE was 3.49 (95% CI, 2.46 to 4.96). Six studies evaluated a total of 48 probands with homozygous FVL variants. The pooled odds ratio for family members of homozygous individuals was 18 (95% CI, 7.8 to 40).

In a larger study of VTE risk in family members, Lijfering et al (2009) pooled results from 5 retrospective family studies of thrombophilia.\textsuperscript{20} A total of 2479 relatives of patients with thrombophilia who were themselves also tested for thrombophilia were included. For relatives with FVL variants, annual incidence of thrombosis was 0.49% (95% CI, 0.39% to 0.60%). In relatives without thrombophilia, incidence of VTE was approximately 0.05% per year, and adjusted relative risk for VTE in relatives with an FVL variant was 7.5 (95% CI, 4.4 to 12.6). In patients treated with anticoagulation, annual risk of major bleeding was 0.29% (95% CI, 0.03% to 1.04%).

**Prothrombin Variants**

Evidence on VTE risk for family members of individuals with a prothrombin variant is lower than for FVL, with 5 studies identified by AHRQ evaluating heterozygotes and only 1 study evaluating homozygotes. For heterozygote probands, family members had an odds ratio for future VTE of 1.89 (95% CI, 0.35 to 10.2).

In the 2009 Lijfering family study, relatives with prothrombin variants had an annual VTE incidence of 0.34% (95% CI, 0.22 to 0.49).\textsuperscript{20} In relatives without thrombophilia, incidence of VTE was approximately 0.05% per year, and adjusted relative risk for VTE in relatives with a prothrombin variant was 5.2 (95% CI, 2.8 to 9.7).

**Pregnancy and Other High-Risk Conditions**

**Pregnancy**
Evidence of the risk of recurrent pregnancy loss in women with FVL or a prothrombin gene variant comprises primarily retrospective case-control studies and cohort studies. Several case-control studies have reported a higher prevalence of FVL in women with recurrent, unexplained pregnancy loss compared with controls (OR range, 2-5). Retrospective cohort studies have found a 2- to 3-fold increased risk of pregnancy loss in FVL heterozygous carriers; homozygotes have a 2-fold higher risk than heterozygous carriers. Risk of pregnancy loss for heterozygous carriers is highest during the second and third trimesters.

A 2012 systematic review by Bradley et al analyzed evidence on the association between FVL and prothrombin variants with pregnancy loss. They identified the highest quality studies, which were cohort studies that: (1) excluded patients with other causes of VTE, (2) tested eligible women for thrombophilia at baseline, (3) reported on subsequent pregnancy outcomes, and (4) compared rates of pregnancy loss between carriers and non-carriers. Four cohort studies met all 4 criteria; these studies primarily included patients with FVL variants. Two of the 4 studies reported a significantly increased rate of recurrence for carriers and 2 did not. Pooled analysis of these 4 studies yielded a significantly increased odds ratio for recurrent pregnancy loss in carriers (OR=1.93; 95% CI, 1.21 to 3.09).

A number of meta-analyses have concluded that the risk of pregnancy loss for patients who are heterozygous for the prothrombin G20210A variant also is increased, in the 2- to 3-fold range.

**Oral Contraceptives**

Oral contraceptive use alone is associated with an approximately 4-fold increase in risk of thrombosis; in combination with FVL, risk multiplies 34-fold in heterozygotes and more than 100-fold in homozygotes. However, the absolute incidence estimated by 1 study published in 1994 was 28 thrombotic events per 10,000 per year, 2% of which were estimated to be fatal.

**Hormone Replacement Therapy**

Women using hormone replacement therapy have a 2- to 4-fold increased risk of thrombosis. Absolute risk is low and may be restricted to the first year of use. Limited data have suggested that women using selective estrogen receptor modulators (e.g., tamoxifen) may have a similarly increased risk.

**Subsection Summary: Clinical Validity**

The clinical validity of genetic testing for thrombophilia has been evaluated by assessing the association between thrombophilia status and VTE in various clinical populations. For populations discussed herein, the clinical validity has been reported in numerous case control and cohort studies. The presence of an FVL or a prothrombin gene variant is associated with an increased risk for subsequent VTE across a number of populations. However, magnitude of the association is relatively modest, with odds ratio most commonly between 1 and 2, except for family members of individuals with inherited thrombophilia, for whom odds ratio are somewhat higher.

**Clinical Utility**

The clinical utility of genetic testing depends on the ability of testing results to change management that results in improved outcomes. The clinical utility of genetic testing for thrombophilia is considered in the context of overall VTE risk and the risk-benefit ratio of treatment, primarily with anticoagulants. The following factors are part of the decision-making process on whether to test for:

- Overall low incidence of thromboembolism in the general population.
- Modest increased risk associated with most forms of inherited thrombophilia, meaning that the absolute risk of thrombosis in patients with inherited thrombophilia is still relatively low.
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- Potential risk of prophylactic treatment, especially bleeding risk with anticoagulation. This risk may outweigh the benefit in patients with a relatively low absolute risk of thrombosis.

Some have suggested that functional testing for activated protein C resistance may be more clinically relevant than genetic testing for FVL in persons with increased risk of thromboembolism.\textsuperscript{23}

**Individuals without a Personal History of VTE**

No published studies identified have directly evaluated the clinical utility of screening asymptomatic individuals for inherited thrombophilia. However, it is unlikely that screening asymptomatic individuals will result in a net health benefit, because prophylactic anticoagulation is likely to do more harm than benefit. Risk of major bleeding with full anticoagulation is approximately 1% per year; therefore, the number of major bleeding episodes may far exceed the number of VTEs prevented. Knowledge of thrombophilia status may lead to behaviors that reduce VTE risk, such as avoidance of prolonged immobility, but this is unproven.

**Individuals with a Personal History of VTE**

The 2008 MEGA study was a large, population-based, case-control study that evaluated whether testing for thrombophilia in patients with a first episode of VTE was associated with a decrease in recurrence rate.\textsuperscript{24} The MEGA database comprised 5051 patients between the ages of 18 and 70 years with a first episode of VTE. Researchers identified 197 patients with a recurrence of VTE and matched these patients by age, sex, year of VTE, and geographic region with 324 patients who were free of recurrent VTE. Recurrence rate for VTE was similar in patients tested for thrombophilia compared with patients who were not tested (OR=1.2; 95% CI, 0.9 to 1.8). The presence of FVL or the prothrombin G20210A variant was not associated with an increased recurrence rate (OR=0.8; 95% CI, 0.3 to 2.6).

Mahajerin et al (2014) conducted a single-center, retrospective cohort study of pediatric patients (mostly adolescents) who presented with VTE (88% deep vein thrombosis) “to help clarify the role of thrombophilia testing in pediatric VTE.”\textsuperscript{25} Of 392 inpatients and outpatients, thrombophilia tests (FVL; prothrombin gene variant; MTHFR; protein C, protein S, and antithrombin activity; antiphospholipid antibodies; plasminogen activator inhibitor-1 levels and variant testing) were ordered in 310 (79%); of these, testing found positive 37 (12%) positive results. Given that most patients had at least 1 risk factor for VTE and, as noted by the authors, the “presence or absence of thrombophilia rarely influences VTE management,” this evidence does not support thrombophilia genetic testing in pediatric patients who present with VTE.

A 2009 study surveyed 112 primary care physicians about the impact of FVL testing in patients with VTE.\textsuperscript{26} Most physicians indicated that they would use results in clinical practice, with 82% reporting that they would use results to counsel patients on risk of recurrence and 67% reporting that they would use results to make treatment changes. However, physician confidence in their decisions was not high, including decisions to order FVL testing.

**Family Members of Individuals with Thrombophilia**

There are no comparative trials of testing versus no testing in relatives of individuals with thrombophilia. The clinical utility of testing depends on the balance between the benefit of altering management as a result of knowledge of variant status and the risk of bleeding with intensification of anticoagulation. This risk-benefit is unknown, as previously discussed. Absolute risk of VTE remains low, even in patients with inherited thrombophilia, and potential risks of prophylactic treatment with anticoagulants may outweigh potential benefits.

**Pregnancy and Other High-Risk Conditions**
No studies have directly evaluated the clinical utility of thrombophilia testing in pregnant women. The clinical utility of testing depends on the efficacy of potential treatments in decreasing fetal loss versus the risks of treatment. Potential treatments in pregnancy include aspirin, low-dose unfractionated or low-molecular-weight heparin, and full-dose heparin. Benefits of these treatments in reducing pregnancy loss are questionable. At least 2 RCTs (both 2010) have reported that there is no significant reduction in risk with aspirin or heparin therapy.\textsuperscript{27,28} Additionally, several meta-analyses have reported that evidence is insufficient to conclude that these interventions reduce recurrent pregnancy loss in patients with FVL or prothrombin variants.\textsuperscript{14,29,30} In contrast, the real risks of anticoagulation include bleeding, thrombocytopenia, and allergic reactions. There also are costs and inconvenience associated with these treatments.

Bradley et al (2012) reviewed the evidence on the clinical utility of testing for heritable thrombophilias in pregnancy and found it adequate to conclude there are no safe and effective treatments to reduce recurrent pregnancy loss in women with inherited thrombophilia.\textsuperscript{14} The certainty of the evidence that treatment resulted in net harm was moderate.

The clinical utility of testing for prothrombin-related thrombophilia was evaluated in a secondary analysis of data from the Stillbirth Collaborative Research Network, a population-based case-control study of stillbirth. Testing for FVL, prothrombin G20210A, methylenetetrahydrofolate reductase C677T, and A1298C, and plasminogen activating inhibitor-1 4G/5G variants was done on maternal and fetal (or placental) DNA from singleton pregnancies. There was an increased odds of stillbirth for maternal homozygous FVL variant (2/488 [0.4%] vs 1/1380 [0.0046%]; OR=87.44; 95% CI, 7.88 to 970.92). However, there were no significant differences in the odds of stillbirth for any other maternal thrombophilia, even after stratified analyses.\textsuperscript{31}

An open-label, international, multicenter randomized trial (2014) of antepartum use of low-molecular weight heparin dalteparin included women with the prothrombin variant. The intervention did not reduce the occurrence of VTE, pregnancy loss, or placenta-mediated pregnancy complications, and was associated with an increased risk of minor bleeding.\textsuperscript{32}

The current chapter (updated in 2014) on prothrombin-related thrombophilia in GeneReviews concluded: “Although technically possible, prenatal diagnosis and preimplantation genetic diagnosis (PGD) are rarely, if ever, performed because the 20210G>A allele only increases the relative risk for thrombophilia and is not predictive of a thrombotic event.”\textsuperscript{16}

Section Summary: Clinical Utility

The clinical utility of testing for FVL or prothrombin variants has not been demonstrated. Although the presence of inherited thrombophilia increases risk for subsequent VTE events, the increase is modest and the absolute risk of thrombosis remains low. Available prophylactic treatments, such as anticoagulation, have defined the risks of major bleeding and other adverse events that may outweigh the reduction in VTE and therefore result in a net harm. Currently available evidence has not defined a role for thrombophilia testing in decisions concerning the initiation of prophylactic anticoagulation or the length of anticoagulation treatment.

SUMMARY OF EVIDENCE

For individuals who are asymptomatic with or without a personal or family history of venous thromboembolism (VTE) or with increased venous thromboembolism risk (e.g., due to pregnancy) who receive genetic testing for variants in 5,10-methylenetetrahydrofolate reductase (MTHFR) gene, coagulation factor V, and coagulation factor II, the evidence includes 1 large RCT, prospective cohort analyses, retrospective family studies, case-control studies, and meta-analyses. Relevant outcomes are morbid events and treatment-related morbidity. The analytic validity of genetic testing for inherited
thrombophilia is high. The analytic sensitivity and specificity for factor V Leiden (FVL) testing both exceed 99%, and the analytic sensitivity and specificity for the prothrombin G20210A variant both exceed 98%. The clinical validity of genetic testing has been demonstrated by the presence of an FVL or a prothrombin gene variant testing and an association with an increased risk for subsequent VTE across various populations studied. However, the magnitude of the association is relatively modest, with odds ratios most commonly between 1 and 2, except for family members of individuals with inherited thrombophilia, for whom odds ratios are somewhat higher. The clinical utility of testing for FVL or prothrombin variants has not been demonstrated. Although the presence of inherited thrombophilia increases risk for subsequent VTE events, the increase is modest and the absolute risk of thrombosis remains low. Available prophylactic treatments (e.g., anticoagulation) have defined risks of major bleeding and other adverse events that may outweigh the reduction in VTE and therefore result in a net harm. Currently available evidence has not defined a role for thrombophilia testing for decisions on initiation of prophylactic anticoagulation or on the length of anticoagulation treatment. For MTHFR testing, clinical validity and clinical utility of genetic testing is uncertain. Because clinical utility of testing for elevated serum homocysteine itself has not been established, utility of genetic testing also has not been established. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

Clinical Input from Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 4 physician specialty societies (6 reviewers) and 6 academic medical centers, for a total of 12 reviewers, while this policy was under review in 2012. Overall, input was mixed, and there was no consensus that genetic testing for thrombophilia was medically necessary for any of the specific clinical situations included. Several reviewers noted that testing could be useful in isolated instances, but were unable to define specific criteria for testing.

PRACTICE GUIDELINES AND POSITION STATEMENTS

Many guidelines and position statements on testing for thrombophilia have been published over the last 2 decades. These guidelines have evolved over time, often do not agree with each other, and do not typically give specific parameters on when to perform genetic testing. The following are examples of U.S. guidelines developed by major specialty societies and published in the last 5 years or so.

Evaluation of Genomic Applications in Practice and Prevention

The 2011 Evaluation of Genomic Applications in Practice and Prevention recommendations did not support the clinical utility of genetic testing for factor V Leiden (FVL) and prothrombin variants for prevention of initial episodes of venous thromboembolism (VTE) or for recurrence. The recommendations have been archived.33

American College of Chest Physicians

The 2016 American College of Chest Physicians (ACCP) guidelines and expert panel report on antithrombotic therapy for VTE disease no longer includes recommendations for pregnant women with known FVL or prothrombin G20210A variants, which had been included in the 2012 edition.34,35 In addition, there are no guidelines on genetic testing for thrombophilia. The 2008 edition indicated that
the presence of a hereditary thrombophilia was not a major factor to guide duration of anticoagulation for VTE.\textsuperscript{36}

**American College of Obstetricians and Gynecologists**

The American College of Obstetricians and Gynecologists published management guidelines for inherited thrombophilias in pregnancy in 2013, which were reaffirmed in 2014.\textsuperscript{4} These guidelines stated that a definitive causal link between inherited thrombophilias and adverse pregnancy outcomes cannot be made. Screening for inherited thrombophilias is controversial, but may be considered for pregnant women in the following situations:

- A personal history of VTE that was associated with a non-recurrent risk factor (e.g., fracture, surgery, or prolonged immobilization).
- A first-degree relative (e.g., parent, sibling) with a history of high-risk thrombophilia.

The guidelines also recommended (as listed in Table 2) the following.

**Table 2. Guidelines for Managing Inherited Thrombophilias During Pregnancy**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Grade</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testing for inherited thrombophilias should include FVL, prothrombin G20210A mutation, and tests for deficiencies in antithrombin, protein S and protein C</td>
<td>C</td>
<td>Consensus and expert opinion</td>
</tr>
<tr>
<td>Testing for inherited thrombophilias in women who have experienced recurrent fetal loss or placental abruption is not recommended because it is unclear whether anticoagulation therapy reduces recurrence</td>
<td>B</td>
<td>Limited or inconsistent scientific evidence</td>
</tr>
<tr>
<td>Because an association between either heterozygosity or homozygosity for the MTHFR C677T polymorphism and any negative pregnancy outcomes, including any increased risk for VTE, has not been shown, screening with either MTHFR mutation analyses or fasting homocysteine levels is not recommended</td>
<td>B</td>
<td>Limited or inconsistent scientific evidence</td>
</tr>
</tbody>
</table>

FVL: factor V Leiden; LOE: level of evidence; VTE: venous thromboembolism.

**American Board of Internal Medicine Foundation**

Choosing Wisely, an initiative of the American Board of Internal Medicine (ABIM) Foundation, seeks to promote discussions between clinicians and patients in order to choose care that is: supported by evidence, not duplicative of other tests or procedures already received, free from harm, and truly necessary. Medical specialty societies and their national organizations have identified tests or procedures commonly used in their field whose necessity should be questioned and discussed. The following medical specialist groups have published contributed recommendations to Choosing Wisely lists specifically related to testing for inherited thrombophilias (see Table 3).\textsuperscript{37}

**Table 3. Medical Society Recommendations on Testing for Inherited Thrombophilias**

<table>
<thead>
<tr>
<th>Society</th>
<th>Year</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASH</td>
<td>2013</td>
<td>“Don’t test for thrombophilia in adult patients with venous thromboembolism (VTE) occurring in the setting of major transient risk factors (surgery, trauma or prolonged immobility).”</td>
</tr>
</tbody>
</table>
“Thrombophilia testing is costly and can result in harm to patients if the duration of anticoagulation is inappropriately prolonged or if patients are incorrectly labeled as thrombophilic. Thrombophilia testing does not change the management of VTEs occurring in the setting of major transient VTE risk factors. When VTE occurs in the setting of pregnancy or hormonal therapy, or when there is a strong family history plus a major transient risk factor, the role of thrombophilia testing is complex and patients and clinicians are advised to seek guidance from an expert in VTE.”

SMFM 2014

“Don’t do an inherited thrombophilia evaluation for women with histories of pregnancy loss, intrauterine growth restriction (IUGR), preeclampsia and abruption.”

“Scientific data supporting a causal association between either methylenetetrahydrofolate reductase (MTHFR) polymorphisms or other common inherited thrombophilias and adverse pregnancy outcomes, such as recurrent pregnancy loss, severe preeclampsia and IUGR, are lacking. Specific testing for antiphospholipid antibodies, when clinically indicated, should be limited to lupus anticoagulant, anticardiolipin antibodies and beta 2 glycoprotein antibodies.”

ASRM 2013

“Don’t routinely order thrombophilia testing on patients undergoing a routine infertility evaluation.”

“There is no indication to order these tests, and there is no benefit to be derived in obtaining them in someone that does not have any history of bleeding or abnormal clotting and in the absence of any family history. This testing is not a part of the infertility workup. Furthermore, the testing is costly, and there are risks associated with the proposed treatments, which would also not be indicated in this routine population.”


U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

MEDICARE NATIONAL COVERAGE

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 4.

Table 4. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
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</table>
### Genetic Testing for Inherited Thrombophilia

<table>
<thead>
<tr>
<th>NCT</th>
<th>Study Title</th>
<th>Study ID Number</th>
<th>Start Date</th>
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<tbody>
<tr>
<td>NCT02385461</td>
<td>Study on Antithrombotic Prevention in Thrombophilia and Pregnancy Loss (OTTILIA)</td>
<td>108</td>
<td>Jun 2017</td>
</tr>
<tr>
<td>NCT02841085</td>
<td>New Genetic Mutations in Thromboembolic Venous Disease Idiopathic</td>
<td>450</td>
<td>May 2018</td>
</tr>
<tr>
<td>NCT02685800</td>
<td>Recurrent Failures in assisted Reproductive Techniques (The FIRST Registry)</td>
<td>624</td>
<td>Sep 2018</td>
</tr>
<tr>
<td>NCT02990403</td>
<td>The Novel Immunomodulatory and Anticoagulant Therapies for Recurrent Pregnancy Loss</td>
<td>500</td>
<td>Dec 2018</td>
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<tr>
<td>NCT02407730</td>
<td>Effects of Thrombophilia on the Outcomes of Assisted Reproduction Technologies</td>
<td>715</td>
<td>Jun 2019</td>
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<tr>
<td>NCT02986594</td>
<td>Diagnosis and Treatment Strategy of Recurrent Spontaneous Abortion Associated With Thrombophilia</td>
<td>600</td>
<td>Oct 2019</td>
</tr>
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</table>

NCT: national clinical trial

### REFERENCES


**CODES**

<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>CPT</td>
<td>81240</td>
<td>F2 (prothrombin, coagulation factor II)(e.g., hereditary hypercoagulability) gene analysis, 20210G&gt;A variant</td>
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<tr>
<td></td>
<td>81241</td>
<td>F5 (coagulation Factor V)(e.g., hereditary hypercoagulability) gene analysis, Leiden variant</td>
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<td>81291</td>
<td>MTHFR (5, 10-methylene tetrahydrofolate reductase)(e.g., hereditary hypercoagulability) gene analysis, common variants (e.g., 677T, 1298C)</td>
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<td></td>
<td>81400</td>
<td>F2 (coagulation factor 2) (eg, hereditary hypercoagulability), 1199G&gt;A variant F5 (coagulation factor V) (eg, hereditary hypercoagulability) HR2 Variant</td>
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<td>Investigational for all relevant diagnoses</td>
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<tr>
<td></td>
<td>D68.51</td>
<td>Activated protein C resistance (includes Factor V Leiden mutation)</td>
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<tr>
<td></td>
<td>D68.52</td>
<td>Prothrombin gene mutation</td>
</tr>
<tr>
<td>ICD-10-CM Code</td>
<td>Description</td>
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<td>----------------</td>
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<tr>
<td>D68.59</td>
<td>Other primary thrombophilia</td>
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<tr>
<td>D68.61-D68.69</td>
<td>Other thrombophilia (includes other hypercoagulable states)</td>
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<tr>
<td>I26</td>
<td>Pulmonary embolism code range</td>
<td></td>
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<tr>
<td>I51</td>
<td>Complications and ill-defined descriptions of heart disease</td>
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</tr>
<tr>
<td>I67.6</td>
<td>Nonpyogenic thrombosis of intracranial venous system</td>
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<tr>
<td>I82.0</td>
<td>Hepatic vein thrombosis</td>
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<tr>
<td>K55.0</td>
<td>Acute vascular disorders of intestine</td>
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<tr>
<td>Z86.718</td>
<td>Personal history of other venous thrombosis and embolism</td>
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<tr>
<td>Z92.0</td>
<td>Personal history of contraception</td>
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</table>

ICD-10-PCS

Not applicable. ICD-10-PCS codes are only used for inpatient services. There are no ICD procedure codes for laboratory tests.

<table>
<thead>
<tr>
<th>Type of service</th>
<th>Place of service</th>
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</thead>
<tbody>
<tr>
<td>Laboratory/ Pathology</td>
<td>Laboratory/ Reference Laboratory</td>
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</tbody>
</table>

**POLICY HISTORY**

<table>
<thead>
<tr>
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</thead>
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<td>07/10/14</td>
<td>Replace policy</td>
<td>Policy updated with literature review through June 19, 2014; references 5-8, 10-11, 24, and 29 added; references 4 and 12 updated. No change to policy statement.</td>
</tr>
<tr>
<td>07/09/15</td>
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</tr>
<tr>
<td>09/15/15</td>
<td>Replace policy</td>
<td>Policy updated with med nec indications for Factor V Leiden indications.</td>
</tr>
<tr>
<td>02/24/17</td>
<td>Replace policy</td>
<td>Added list of investigational tests for inherited thrombophilic disorders in the evaluation of recurrent pregnancy loss.</td>
</tr>
<tr>
<td>06/01/17</td>
<td>Replace policy</td>
<td>Policy updated with literature review through April 12, 2017; references 29-32, 34, and 37. The policy is revised with updated genetics nomenclature; “mutations” changed to “variants” throughout policy. Policy statement otherwise unchanged.</td>
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<tr>
<td>04/30/18</td>
<td>Update only</td>
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<tr>
<td>05/30/18</td>
<td>Replace policy</td>
<td>Blue Cross of Idaho updated policy with literature review through March 5, 2018; no references added; reference 3 updated. Policy statement unchanged.</td>
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</table>
### APPENDIX

<table>
<thead>
<tr>
<th>Category</th>
<th>Addressed</th>
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<tbody>
<tr>
<td>1. Testing of an affected individual’s germline to benefit the individual</td>
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</tr>
<tr>
<td>1a. Diagnostic</td>
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</tr>
<tr>
<td>1b. Prognostic</td>
<td></td>
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<tr>
<td>1c. Therapeutic</td>
<td></td>
</tr>
<tr>
<td>2. Testing cancer cells from an affected individual to benefit the individual</td>
<td></td>
</tr>
<tr>
<td>2a. Diagnostic</td>
<td></td>
</tr>
<tr>
<td>2b. Prognostic</td>
<td></td>
</tr>
<tr>
<td>2c. Therapeutic</td>
<td></td>
</tr>
<tr>
<td>3. Testing an asymptomatic individual to determine future risk of disease</td>
<td>X</td>
</tr>
<tr>
<td>4. Testing of an affected individual’s germline to benefit family members</td>
<td></td>
</tr>
<tr>
<td>5. Reproductive testing</td>
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<tr>
<td>5a. Carrier testing: preconception</td>
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<tr>
<td>5b. Carrier testing: prenatal</td>
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<tr>
<td>5c. In utero testing: aneuploidy</td>
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<td>5d. In utero testing: mutations</td>
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</tr>
<tr>
<td>5e. In utero testing: other</td>
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<tr>
<td>5f. Preimplantation testing with in vitro fertilization</td>
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</tbody>
</table>