Clinical Policy Title: Genetic testing for G1691A polymorphism: factor V Leiden

Clinical Policy Number: Not yet assigned

Effective Date: January 1, 2016
Initial Review Date: July 15, 2015
Most Recent Review Date: August 19, 2015
Next Review Date: July 2016

Related policies:

- CP# 02.01.01 Maternal genetic testing
- CP# 02.01.02 Genetic testing for breast and ovarian cancer
- CP# 02.01.04 Pharmacogenetic testing for warfarin
- CP# 02.01.08 Familial polyposis gene testing
- CP# 02.01.09 Genetic testing, rare diseases
- CP# 02.01.11 Afirma gene expression classifier for indeterminate thyroid nodules
- CP# 02.01.14 Gene expression profile testing for breast cancer
- CP# 05.01.01 Viral oncogene mutation testing
- CP#13.01.01 Genetic testing for prostate cancer prognosis

ABOUT THIS POLICY: Arbor Health Plan has developed clinical policies to assist with making coverage determinations. Arbor Health Plan’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by Arbor Health Plan when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Arbor Health Plan’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Arbor Health Plan’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Arbor Health Plan will update its clinical policies as necessary. Arbor Health Plan’s clinical policies are not guarantees of payment.

Coverage policy

Arbor Health Plan considers the use of genetic testing for factor V Leiden to be clinically unproven and, therefore, not medically necessary.

Limitations:

All uses of genetic testing for factor V Leiden are not medically necessary.
Alternative covered services:

Routine laboratory tests for coagulopathy may be ordered by a family practice or primary physician.

Background

The protein product of the factor V gene G1691A is the natural thrombophilic agent factor V Leiden (FVL). Elevated blood concentrations of FVL are associated with an increased initial risk of thrombosis (i.e., in the homozygous individual) and of recurrence of thrombosis. Heterozygous individuals are also at increased for thrombus, but much less so than their homozygous counterparts. There is conjecture that screening for FVL may identify individuals at high risk for future thromboembolism and thus aid in selection of at-risk individuals for prophylactic anti-coagulant therapy. The status of FVL zygosity also impacts the likelihood of idiopathic venous thromboembolism (VTE). Finally, as VTE and cancer are frequently observed together, there is conjecture that identification of FVL may focus screening for malignancy.

Searches

Arbor Health Plan searched PubMed and the databases of:

- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on June 24, 2015, using the terms "Leiden (MeSH)," "factor V (MeSH)" and "genetic test (MeSH)." We included:

- Systematic reviews, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- Guidelines based on systematic reviews.
- Economic analyses, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

Findings

The American College of Chest Physicians Evidence-based Clinical Practice Guidelines (ACCP 2012) address the use of low-molecular weight heparin (LMWH) for antepartum prophylaxis in pregnant women with no personal history of VTE but whose family history is affirmative for VTE, and who are homozygous for FVL. The guidelines suggest antepartum and post-partum prophylaxis for six weeks in these individuals. In the absence of family history of VTE the guidelines recommend antepartum observation and post-partum prophylaxis for six weeks with LMWH.
The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group did not find enough evidence of change in physician management of VTE to recommend routine testing for FVL (EGAPP 2012). EGAPP added that potential benefits are unlikely to exceed potential harms. The recommendations do not extend to patients with other risk factors for thrombosis (e.g., contraceptive use).

Pernod (2009) came to a similar conclusion, observing that the etiology of VTE is complex and FVL zygosity only one of numerous variables at work in thrombophilia disorders.

Finally, Lijfering (2009) studied various blood clotting factors and found FVL to be among the least of several causes of clinical VTE. Hereditary deficiencies of antithrombin, protein C and protein S were of greater clinical significance compared to FVL testing.

For cancer screenings, there is modest evidence (Robertson 2015) that identification of cancer occurs earlier and the cancer is less advanced when VTE screening is employed. Unfortunately, the pertinent studies in this regard did not indicate FVL zygosity.

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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<tbody>
<tr>
<td>Robertson (2015)</td>
<td><strong>Key points:</strong>&lt;br&gt;• SR of only two RCTs inclusive of 396 patients with previous VTE.&lt;br&gt;• Screening with non-genetic tests found malignancies were less advanced in screened group vs. unscreened controls.&lt;br&gt;• Screened patients were diagnosed with cancer earlier (mean one month versus 11 months).&lt;br&gt;• Study did not indicate FVL zygosity.</td>
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<td>ACCP (2012)</td>
<td><strong>Key points:</strong>&lt;br&gt;• Prevention of VTE in pregnant women with thrombophilia and no prior VTE.&lt;br&gt;• For pregnant women with no prior history of VTE known to be homozygous for FVL or the prothrombin 20210A mutation who have a positive family history for VTE, we suggest antepartum prophylaxis with prophylactic- or intermediate-dose LMWH and postpartum prophylaxis for six weeks with prophylactic- or intermediate-dose LMWH, or VKAs targeted at INR 2.0 to 3.0, rather than no prophylaxis (Grade 2B). (.9.2.1.)&lt;br&gt;• For pregnant women with all other thrombophilias and no prior VTE who have a positive family history for VTE, we suggest antepartum clinical vigilance and postpartum prophylaxis with prophylactic- or intermediate-dose LMWH; or, in women who are not protein C or S deficient, VKAs targeted at INR 2.0 to 3.0, rather than routine care (Grade 2C). (.9.2.2.)&lt;br&gt;• For pregnant women with no prior history of VTE known to be homozygous for FVL or the prothrombin 20210A mutation and who do not have a positive family history for VTE, we suggest antepartum clinical vigilance and postpartum prophylaxis for six weeks with prophylactic- or intermediate-dose LMWH or VKAs targeted at INR 2.0 to 3.0, rather than routine care (Grade 2B). (.9.2.3.)&lt;br&gt;• For pregnant women with all other thrombophilias and no prior VTE who do not have a positive family history for VTE, we suggest antepartum and postpartum clinical vigilance, rather than pharmacologic prophylaxis (Grade 2C). (.9.2.4.)</td>
</tr>
<tr>
<td>EGAPP (2011)</td>
<td><strong>Key points:</strong>&lt;br&gt;• Routine testing for FVL not recommended in persons with idiopathic VTE.</td>
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</table>
Routine testing for FVL not recommended in family members of persons with idiopathic VTE.
Risks exceed harms.
As idiopathic VTE was the only disease studied, no conclusions were made about other risk factors for disease (e.g., users of oral contraceptives).

Pernod (2009)
Key points:
- Thrombosis is multi-factorial and FVL zygosity only one component.
- However, screening is indicated with proximal idiopathic VTE in persons < 60 years old and in women with any VTE of child-bearing age.

Makris (2009)
Key points:
- In a retrospective family cohort, where probands had thrombosis and a thrombophilic defect, 2,479 relatives were tested for thrombophilia.
- Annual incidence of venous thrombosis in relatives with FVL was 0.49% (95% CI, 0.39-0.60).
- In antithrombin-, protein C-, and protein S-deficient relatives, annual incidences of venous thrombosis were 1.77% (95% CI, 1.14–2.60), 1.52% (95% CI, 1.06–2.11), and 1.90% (95% CI, 1.32–2.64).

Glossary

Deep venous thrombosis (DVT) — The formation of a blood clot (thrombus) within a deep vein.

Pulmonary embolism (PE) — A blockage of the lung's main artery or one of its branches by a substance that has traveled from elsewhere in the body through the bloodstream (embolism).

Venous thromboembolism (VTE) — Includes both DVT and PE.

References

Professional society guidelines/others:


Peer-reviewed references:

Clinical trials:


CMS National Coverage Determinations (NCDs):


Local Coverage Determinations (LCDs):


Indications:
Molecular pathology procedures (Tier1 and Tier 2) may be eligible for coverage when ALL of the following criteria are met:

• Alternative laboratory or clinical tests to definitively diagnose the disorder/identify the condition are unavailable or results are clearly equivocal;
  AND
• Availability of a clinically valid test, based on published peer reviewed medical literature;
  AND
• Testing assay(s) are Food and Drug Administration (FDA) approved/cleared or if LDT (lab developed test) or LDT protocol or FDA modified test(s) the laboratory documentation should support assay(s) of analytical validity and clinical utility;
  AND
• Results of the testing must directly impact treatment or management of the Medicare beneficiary;
  AND
• For testing panels, including but not limited to, multiple genes or multiple conditions, and in cases where a tiered approach/method is clinically available, testing would be covered ONLY for the number of genes or test that are reasonable and necessary to obtain necessary information for therapeutic decision making; AND
• Individual has not previously received genetic testing for the disease/condition. (In general, diagnostic genetic testing for a disease should be performed once in a lifetime.)

Commonly Submitted Codes
Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill in accordance with those manuals.

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<td>CYP2C19 (cytochrome P450 family2, subfamily C, polypeptide 19) (eg, drug metabolism, gene analysis, common variants)</td>
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