Subject: Genetic Testing: Hypercoagulability/Thrombophilia

Medical Policy #: 7.11

Original Effective Date: 03-24-2021

Status: Reviewed

Last Annual Review Date: 03-26-2025

Disclaimer

Refer to the member's specific benefit plan and Schedule of Benefits to determine coverage. This may not be a benefit on all plans or the plan may have broader or more limited benefits than those listed in this Medical Policy.

Description

Factor V Leiden thrombophilia, the most common inherited form of thrombophilia, is an inherited disorder of the F5 gene that results in resistance to activated protein C and a predisposition to venous thromboembolism.
Factor II Prothrombin thrombophilia, the second most common genetic risk factor for venous thromboembolism after factor V Leiden thrombophilia.

Coverage Determination

Prior Authorization is required. Logon to Pres Online to submit a request: https://ds.phs.org/preslogin/index.jsp

Coverage Determinations:

The following two germline hereditary mutation tests will be considered medically reasonable and necessary when performed for evaluation of venous thromboembolism.

- Factor II (F2 gene)
- Factor V (F5 gene)

For Commercial members:
Presbyterian Health Plan follows MCG criteria (ACG: A-0600) for F5 Gene; and (ACG: A-0613) for F2 Gene coverage.

For non-coverage of Hyperhomocysteinemia -MTHFR Gene, see MCG criteria (A-0629). Presbyterian Health Plan utilizes the Care Guidelines to determine medical necessity for the plans that we manage. The Guidelines are the protected intellectual property of MCG. Presbyterian Health Plan is not able to distribute them without the permission of MCG. MCG has provided a tool that allows Presbyterian Health Plan members and prospective members to view relevant MCG guidelines, however you will not be able to print them.

For Medicare and Medicaid members:
Presbyterian Health Plan follows CMS Novitas Biomarkers Overview, LCD (L35062) and related article (A56541), for Factor II and for Factor V coverage.

- The Medicare benefit applies only to individuals with signs and symptoms of disease. There is no Medicare benefit for assessment of thrombosis risk in asymptomatic patients (aka screening for inherited thrombophilia) or in asymptomatic individuals whose relatives have documented inherited thrombophilia

For non-coverage of MTHFR see CMS, WPS MolDX: Genetic Testing for Hypercoagulability/Thrombophilia (Factor V Leiden, Factor II Prothrombin, and MTHFR), LCD (L36400) and related article (A57571).

Limitations:
Repeat Germline Testing for codes (81240 and 81241) more than once in a lifetime is non-covered. PHP follows WPS, LCD (L38429)-Repeat Germline Testing. *"Germline testing is differentiated from somatic testing in that somatic testing identifies alterations specific to an individual cell or group of cells derived from that cell (such as a neoplasm or clonal hematopoietic cells) whereas germline testing seeks to identify inherited variants or alleles that are present in all the patient's cells and make up a baseline genetic code of the individual. Although somatic alterations are constantly occurring during the life of an individual, the germline sequence of an individual does not change over time."*

Testing for inherited thrombophilia in individuals who have experienced recurrent fetal loss or placental abruption is not covered because it is unclear if anticoagulation therapy reduces recurrence.

There is a broad consensus in the medical literature that MTHFR genotyping (CPT 81291) has no clinical utility in any clinical scenario. This test is considered investigational and is not a Medicare, Commercial or Medicaid benefit.

Coding

The coding listed in this medical policy is for reference only. Covered and non-covered codes are within this list.

CPT Codes	Description
81240	F2 (prothrombin, coagulation factor II) (eg, hereditary hypercoagulability) gene analysis, 20210G>A variant
81241	F5 (coagulation factor V) (eg, hereditary hypercoagulability) gene analysis, Leiden variant

ICD-10 CODE	ICD-10 for Medicare ONLY
Refer to ICD-10 Code Group 1 in the related Local Coverage Article: Billing and Coding: Biomarkers Overview (A56541).	

Reviewed by / Approval Signatures

Population Health and Clinical Quality Committee (PHCQC): Clinton White MD
Senior Medical Directory: Jim Romero MD
Date Approved: 03-26-2025

References

1. CMS, WPS, (LCD): MolDX: Genetic Testing for Hypercoagulability Thrombophilia (Factor V Leiden, Factor II Prothrombin, and MTHFR) (L36400), Revision date: 07/20/2023, R#7. Related policy article A57571, revision date 07/27/2023, R2. [Cited 02-20-2025]
2. MCG, 28th Edition, Factor V Leiden Thrombophilia – F5 Gene, (ACG: A-0600), last updated 3/14/2024 . [Cited 02-20-2025]
3. MCG, 28th Edition, Prothrombin Thrombophilia – F2 Gene, ACG: A-0613, Last update 3/14/2024 . [Cited 02-20-2025].
4. MCG, 28th Edition, Hyperhomocysteinemia – MTHFR Gene, (ACG: A-0629), Last Update: 3/14/2024 . [Cited 02-20-2025]
5. ACOG Practice Bulletin, Inherited Thrombophilias in Pregnancy, ACOG Practice Bulletin No. 197. Obstetrics & Gynecology 2018 (ACOG reaffirmed 2020);132(1):e18-e34. DOI: 10.1097/AOG.0000000000002703. (Reaffirmed 2022 Jul). [Cited 02/20/2025]
6. CMS, LCD Biomarkers Overview (L35062), Revision 22, revision date: 12/12/2021. Related policy article LCA A56541, Revised 01-01-2024 R6. [Cited 02/20/2025]
7. Hayes, MTHFR Genetic Testing for Severe MTHFR Enzyme Deficiency, Clinical Utility Evaluation, Sep 19, 2024 | GERMLINE. [Cited 02-20-2025]
8. Hayes, *MTHFR* Genetic Testing for Hypertension, Clinical Utility Evaluation, Dec 09, 2024 | GERMLINE. [Cited 02/20/2025]
9. Hayes, MTHFR Genetic Testing for Pregnancy Complications**,** Clinical Utility Evaluation, Dec 9, 20241 | GERMLINE. [Cited 02/20/2025]
10. Hayes, Genetic Testing for Common Forms of Hereditary Thrombophilia in Pediatric Patients with Unprovoked Venous Thromboembolism, Clinical Utility Evaluation, Jun 21, 2022 | Annual Review: Jun 21, 2022 | GERMLINE. [Cited 02/20/2025]
11. Hayes, Genetic Testing for Common Forms of Hereditary Thrombophilia in Adults With Unprovoked Venous Thromboembolism, Clinical Utility Evaluation, May 21, 2019 | Annual Review: Jun 21, 2022 | GERMLINE. [Cited 02/20/2025]
12. Hayes, Genetic Testing for Factor V Leiden in Women with Unexplained Recurrent Pregnancy Loss, Clinical Utility Evaluation, Dec 19, 2019 | Annual Review: Oct 24, 2022 | GERMLINE. [Cited 02/24/2025]
13. CMS, WPS, LCD (L38429)- REPEAT Germline Testing, Revision Date 04-25-2024, R3. Related article CGS, (A57100), revision date 01/01/2025, R13 [Cited 02-20-2025]
14. HCA, Letter of Direction (LOD)#42- Biomarker Coverage, Date: December 20, 2024 [Cited 02/28/2025]

Publication History

03-24-21	New policy. Reviewed by PHP Medical Policy Committee on 02/10/2021. Thrombosis panel for risk assessment for venous thromboembolism was moved from MPM 7.1. Non-Medicare members will follow MCG A-0613 (for F-II) and MCG A-0600 (for F-V). Medicare will follow LCD L36400 and L35062. Set 81240 and 81241 to pay only for Medicare with those ICD-10 listed in CMS LCA A56541. Set 81291 to not pay due to investigational for all LOB because "There is broad consensus in the medical literature that MTHFR genotyping has no clinical utility in any clinical scenario."
03-23-22	Annual review: Reviewed by PHP Medical Policy Committee on 03-02-2022. No change. Continue Non-Medicare to follow MCG A-0613 (for F-II) and MCG A-0600 (for F-V). Medicare will continue to follow LCD L36400 and L35062. Continue with the configuration of 81240 and 81241 to link (111) ICD-10 codes listed in

	A56541 in Group 1 and continue PA requirement for 81240 and 81241. MTHFR genotyping (code 81291) will be removed from PA grid and will be listed in the Investigative List (non-Covered Services), MPM 36.0, since it is still considered investigational.
03-22-23	Annual review: Reviewed by PHP Medical Policy Committee on 01/25/2023. No change to the overall policy regarding criteria. For non-Medicare section, added MCG (A-0629) to support non-coverage of MTHFR. Reformatted the policy. Previous config requested in CY 2021 for codes (81240 and 81241) to link to (111) ICD-10 listed in Novitas LCA (A56541) in Group 1 will be submitted. Continue previous configuration of 81291 to not pay due to investigational for all LOB. Continue the configuration to require prior authorization of 81240 and 81241, unless billed by a Hematology/Oncology provider. Removed code 81291, see MPM 36.0.
03-24-24	Annual review: Reviewed by PHP Medical Policy Committee on 02/15/2024. There is no change in coverage. Non-Medicare will continue to follow MCG for both covered and non-covered tests. For Medicare continue to follow both Novitas and WSP LCD and LCA for both covered and non-covered tests. Continue configuration of 81291 (MTHFR) to not pay for all LOB, since it is still considered investigational. Updated configuration to include UB claims for 81291. Continue current configuration for 81240 (F2) and 81241 (F5) to only pay for listed DX in Novitas LCA A56541 for ALOB. Updated config to include commercial and Medicaid for 81240/41 because it was not done. Continue prior authorization of 81240 and 81241, unless billed by a Hematology/Oncology provider.
03-26-25	Annual review: Reviewed by PHP Medical Policy Committee on 02-28-2025. The only change is Medicaid line of business that was moved and/or reformatted to be under CMS LCD guidance to confer with Biomarker Coverage Letter of Direction (LOD#42) that was released in Dec 2024. Otherwise, there is no change in coverage criteria for 81240 (F2) and 81241 (F5); and no change for the non-coverage of MTHFR (81291). Language was added to the policy to support the “once in a lifetime” for Factor 2 and Factor 5. Continue config for MTHFR (81291) as investigational and experimental. Continue prior authorization of 81240 and 81241, unless billed by a Hematology/Oncology provider. Continue to have Optum configure (which includes Pro-fee and UB facility) codes (81240 and 81241) to pay for (111) diagnosis listed in Group 1 Paragraph per LCA (A56541) for ALOB that was submitted on 02/20/2024. Continue config for 81240 and 81241 as *once in a lifetime*.

This Medical Policy is intended to represent clinical guidelines describing medical appropriateness and is developed to assist Presbyterian Health Plan and Presbyterian Insurance Company, Inc. (Presbyterian) Health Services staff and Presbyterian medical directors in determination of coverage. The Medical Policy is not a treatment guide and should not be used as such.

For those instances where a member does not meet the criteria described in these guidelines, additional information supporting medical necessity is welcome and may be utilized by the medical director in reviewing the case. Please note that all Presbyterian Medical Policies are available online at: ***Click here for Medical Policies***

Web links:

At any time during your visit to this policy and find the source material web links has been updated, retired or superseded, PHP is not responsible for the continued viability of websites listed in this policy.

When PHP follows a particular guideline such as LCDs, NCDs, MCG, NCCN etc., for the purposes of determining coverage; it is expected providers maintain or have access to appropriate documentation when requested to support coverage. See the References section to view the source materials used to develop this resource document.