

Clinical Policy: Genetic Testing Hematologic Condition (non-cancerous)

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[Coding Implications](#)

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See [Important Reminder](#) at the end of this policy for important regulatory and legal information.

Description

Genetic testing for hematologic (non-cancerous) conditions may be used to confirm a diagnosis in a patient who has signs and/or symptoms of a specific hematologic condition. Confirming the diagnosis may alter aspects of management and may eliminate the need for further diagnostic workup. This document addresses genetic testing for common hematologic (non-cancerous) conditions.

Below is a list of higher volume tests and the associated laboratories for each criteria section. This list is not all inclusive.

CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
81403	Targeted Mutation Analysis for a Known Familial Variant	Known Familial Variant Analysis	N/A
81241	F5 R506Q Targeted Mutation Analysis	Factor V Leiden (F5) and Prothrombin (F2) Variant Analysis for Inherited Thrombophilia	D68.51, D68.2, D68.59, Z86.2, I82.90
81240	F2 G20210A Targeted Mutation Analysis	Factor V Leiden (F5) and Prothrombin (F2) Variant Analysis for Inherited Thrombophilia	D68.52, D68.2, R79.1, I82.409
81257, 81259, 81269, S3845, S3850	HBA1 Deletion/Duplication Analysis HBA2 Deletion/Duplication Analysis HBA1 Sequencing Analysis HBA2 Sequencing Analysis	HBA1/HBA2 and/or HBB Variant Analysis	D56.0, D56.9, D53.9, R70.1, D56.3, D56.8, Z86.2

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CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
81361, 81362, 81363, 81364, 81479, S3846	HBB Sequencing Analysis HBB Deletion/Duplication Analysis HBB Targeted Mutation Analysis	HBA1/HBA2 and/or HBB Variant Analysis	D57.00-D57.819, D56.1, D64.9, R53.83
81238, 81403, 81406, 81407, 81479	F8 Targeted Mutation Analysis F8 Deletion/Duplication Analysis F8 Sequencing Analysis F9 Targeted Mutation Analysis F9 Deletion/Duplication Analysis F9 Sequencing Analysis	F8 and/or F9 Variant Analysis	D66, I62.9, M25, N92.2, R04.0, R31
81247, 81248, 81249	G6PD Targeted Mutation Analysis G6PD Sequencing Analysis	G6PD Variant Analysis	D55.0
81401, 81403, 81405, 81408, 81479	GP1BA Triple Exon Analysis VWF Triple Exon Analysis Von Willebrand Disease Genetic Analysis	GP1BA and/or VWF Variant Analysis	D68.0
81400-81408	See list below	Other Hematologic Conditions (non-cancerous)	N/A

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This policy document provides criteria for Genetic Testing for Hematologic Conditions (Non-Cancerous). Please refer to:

- ***CP.MP.241 Oncology: Molecular Analysis of Solid Tumors and Hematologic Malignancies*** for criteria related to exome and genome sequencing of solid tumors and hematologic malignancies.
- ***CP.MP.234 Genetic Testing: Prenatal and Preconception Carrier Screening*** for criteria related to carrier screening in the prenatal, preimplantation, and preconception setting.
- ***CP.MP.235 Genetic Testing: Prenatal Diagnosis (via amniocentesis, CVS, or PUBS) and Pregnancy Loss*** for related to prenatal and pregnancy loss diagnostic genetic testing for tests intended to diagnose genetic conditions following amniocentesis, chorionic villus sampling or pregnancy loss.
- ***CP.MP.230 Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay*** for criteria related to diagnostic genetic testing for conditions affecting multiple organ systems.
- ***CP.MP.229 Genetic Testing: Metabolic, Endocrine, and Mitochondrial Disorders*** for criteria related to genetic testing for *MTHFR*.
- ***CP.MP.222 Genetic Testing: General Approach to Genetic Testing*** for criteria related to genetic testing for non-cancerous hematologic disorders that are not specifically discussed in this or another non-general policy.

Policy/Criteria

Known Familial Variant Analysis for Hematologic Conditions (Non-Cancerous)

- I. It is the policy of health plans affiliated with Centene Corporation[®] that targeted mutation analysis for a known familial variant (81403) for a non-cancerous hematologic condition is considered **medically necessary** when:
 - A. The member/enrollee has a [close relative](#)¹ with a known pathogenic or likely pathogenic variant causing the condition.
- II. It is the policy of health plans affiliated with Centene Corporation[®] that current evidence does not support targeted mutation analysis for a known familial variant (81403) for a non-cancerous hematologic condition for all other indications.

Inherited Thrombophilia

Factor V Leiden (*F5*) and Prothrombin (*F2*) Variant Analysis for Inherited Thrombophilia

- I. It is the policy of health plans affiliated with Centene Corporation[®] that *F5* (81241) and *F2* (81240) variant analysis to confirm or establish a diagnosis of an inherited thrombophilia may be considered **medically necessary** when:
 - A. The member/enrollee meets at least one of the following:
 1. A first unprovoked venous thromboembolism (VTE) <50 years old,

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2. VTE at unusual sites (such as hepatic portal, mesenteric, and cerebral veins),
 3. Recurrent VTE,
 4. Personal history of VTE with:
 - a) two or more [close relatives](#)¹ with a history of VTE,
 - b) one [first-degree](#)^{1a} [relative](#) with VTE at a young age,
 5. Low activated protein C (APC) resistance activity
- II. It is the policy of health plans affiliated with Centene Corporation[®] that current evidence does not support *F5* (81241) and *F2* (81240) variant analysis to confirm or establish a diagnosis of an inherited thrombophilia for all other indications.

Hemoglobinopathies

HBA1/HBA2 and/or *HBB* Variant Analysis

- I. It is the policy of health plans affiliated with Centene Corporation[®] that *HBA1/HBA2* variant analysis (81257, 81258, 81259, 81269, S3845), and/or *HBB* (81361, 81362, 81363, 81364, 81479, S3846, S3850) to confirm or establish a diagnosis of a hemoglobinopathy (e.g., alpha-thalassemia, beta-thalassemia, or sickle cell disease) is considered **medically necessary** when meeting either of the following:
 - A. The member/enrollee's hematologic screening results (e.g., MCV, MCH, CBC, hemoglobin electrophoresis, or dichlorophenol indophenol (DCIP)) are positive for a hemoglobinopathy,
 - B. The member/enrollee's hematologic screening results (e.g., MCV, MCH, CBC, hemoglobin electrophoresis, or dichlorophenol indophenol (DCIP)) do not conclusively diagnose or rules out a hemoglobinopathy.
- II. It is the policy of health plans affiliated with Centene Corporation[®] that current evidence does not support *HBA1/HBA2* variant analysis (81257, 81258, 81259, 81269, S3845), and/or *HBB* (81361, 81362, 81363, 81364, 81479, S3846, S3850) to confirm or establish a diagnosis of a hemoglobinopathy (e.g., alpha-thalassemia, beta-thalassemia, or sickle cell disease) for all other indications.

Hemophilia

F8 and/or *F9* Variant Analysis

- I. It is the policy of health plans affiliated with Centene Corporation[®] that *F8* variant analysis (81403, 81406, 81407) and/or *F9* variant analysis (81238, 81479) to confirm or establish a diagnosis of hemophilia A or B is considered **medically necessary** when meeting any of the following:
 - A. The member/enrollee has any of the following clinical features of hemophilia:

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1. Hemarthrosis (especially with mild or no antecedent trauma)
2. Deep-muscle hematomas
3. Intracranial bleeding in the absence of major trauma
4. Neonatal cephalohematoma or intracranial bleeding
5. Prolonged oozing or renewed bleeding after initial bleeding stops following tooth extractions, mouth injury, or circumcision
6. Prolonged or delayed bleeding or poor wound healing following surgery or trauma
7. Unexplained GI bleeding or hematuria
8. Heavy or prolonged menstrual bleeding (especially with onset at menarche)
9. Prolonged nosebleeds, especially recurrent and bilateral
10. Excessive bruising (especially with firm, subcutaneous hematomas),

B. All of the following laboratory features:

1. Normal platelet count,
2. Prolonged activated partial thromboplastin time (aPTT),
3. Normal prothrombin time (PT)

- II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support *F8* variant analysis (81403, 81406, 81407) and/or *F9* variant analysis (81238, 81479) to confirm or establish a diagnosis of hemophilia A or B for all other indications.

Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency

G6PD Variant Analysis

- I. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support *G6PD* variant analysis (81247, 81248, 81249) to confirm or establish a diagnosis* of glucose-6-phosphate dehydrogenase deficiency.

* Diagnosis of G6PD can be achieved by quantitative spectrophotometric analysis or, more commonly, by a rapid fluorescent spot test detecting the generation of NADPH from NADP.

Von-Willebrand Disease

GP1BA and *VWF* Variant Analysis

- I. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support *GP1BA* and/or *VWF* variant analysis (81401, 81403, 81405, 81408) to confirm or establish a diagnosis* of von-Willebrand disease.

* Diagnosis of von-willebrand disease can be achieved by standard laboratory and biochemical testing.

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Other Hematologic Conditions (non-cancerous)

The following is a list of conditions that have a known genetic association. Due to their relative rareness, these genetic tests may be appropriate to establish or confirm a diagnosis.

- I. It is the policy of health plans affiliated with Centene Corporation[®] that genetic testing to establish or confirm one of the following hematologic conditions (non-cancerous) to guide management is considered **medically necessary** when the member/enrollee demonstrates clinical features* consistent with the disorder (the list is not meant to be comprehensive, see II below):

- A. [Atypical Hemolytic-Uremic Syndrome \(aHUS\)](#)
- B. [Complete Plasminogen Activator Inhibitor 1 Deficiency \(PAI-1\)](#)
- C. [Diamond-Blackfan Anemia \(DBA\)](#)
- D. [Hereditary Spherocytosis](#)
- E. Factor VII Deficiency
- F. Factor X Deficiency
- G. Factor XI Deficiency (Hemophilia C)
- H. Factor XII Deficiency
- I. Factor XIII Deficiency

- II. It is the policy of health plans affiliated with Centene Corporation[®] that genetic testing to establish or confirm the diagnosis of all other non-cancerous hematologic conditions not specifically discussed within this or another medical policy will be evaluated by the criteria outlined in *CP.MP.222 General Approach to Genetic Testing* (see policy for criteria).

*Clinical features for a specific disorder may be outlined in resources such as [GeneReviews](#), [OMIM](#), [National Library of Medicine, Genetics Home Reference](#), or other scholarly source.

Notes and Definitions

1. Close relatives include first, second, and third degree blood relatives on the same side of the family:
 - a. **First-degree relatives** are parents, siblings, and children
 - b. **Second-degree relatives** are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half siblings
 - c. **Third-degree relatives** are great grandparents, great aunts, great uncles, great grandchildren, and first cousins

Background

Genetic Testing for Hemoglobinopathies

Viprakasit V, Ekwattanakit S (2018) published a clinical classification, screening and diagnosis for thalassemia article that poses:

“In general, these mutation analyses would be critical for the confirmation of thalassemia diagnoses in only a few selected cases for whom the basic hematology and Hb analysis described could not provide a conclusive diagnosis. However, these molecular analyses

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would be indispensable in a program for the prevention and control of thalassemia syndromes because the mutation data would be required for genetic counseling, genetic risk calculation in the offspring, and prenatal and preimplantation genetic diagnosis. In addition, DNA analysis could help in predicting the clinical severity and guiding clinical management; milder b-globin mutations (b1-thal) usually are associated with milder phenotypes, as has been shown in HbE/b-thalassemia.”

Genetic Testing for Alpha Thalassemia

American College of Obstetricians and Gynecologists

The American College of Obstetricians and Gynecologists (2017) published an opinion document that includes multiple general recommendations about carrier screening of genetic conditions. Specific descriptions of genetic testing for α -thalassemia include the following: DNA-based genetic testing should be used to detect a-globin gene characteristics of suspected cases of thalassemia “[i]f the mean corpuscular volume is below normal, iron deficiency anemia has been excluded, and the hemoglobin [Hb] electrophoresis is not consistent with b-thalassemia trait (ie, there is no elevation of Hb A2 or Hb F).

Genetic Testing for Inherited Thrombophilia

American Board of Internal Medicine Foundation- Choosing Wisely Campaign

Choosing Wisely, an initiative of the American Board of Internal Medicine Foundation seeks to promote discussions between clinicians and patients 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 contributed recommendations to *Choosing Wisely* lists specifically related to testing for inherited thrombophilias (see Table 1).

Table 1. Medical Society Recommendations on Testing for Inherited Thrombophilia

Society	Year	Recommendation
American Society of Hematology	2013	“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).”
		“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.”

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Society for Maternal-Fetal Medicine	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.”
American Society for Reproductive Medicine	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.”

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (2018) published updated technical standards for genetic testing for variants associated with VTE, with a focus on factor V Leiden and factor II. The standards do not make recommendations on the indications for testing, and the authors note that testing indications from different professional organizations vary.

American College of Obstetricians and Gynecologists

The American College of Obstetricians and Gynecologists (2013) published management guidelines for inherited thrombophilias in pregnancy, which were reaffirmed in 2014 and in 2018. These guidelines stated the following:

- “A definitive causal link between inherited thrombophilias and adverse pregnancy outcomes could not be made.”
- “Screening for inherited thrombophilias is controversial, but may be considered for pregnant women in the following situations:
 - A personal history of VTE associated with a nonrecurrent risk factor (eg, fracture, surgery, or prolonged immobilization).
 - A first-degree relative (eg, parent, sibling) with a history of high-risk thrombophilia.
 Guidelines for Managing Inherited Thrombophilias During Pregnancy”

Evaluation of Genomic Applications in Practice and Prevention

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

Genetic Testing for Glucose-6 Phosphate Dehydrogenase (G6PD) Deficiency

American Academy of Family Physicians

“The diagnosis of G6PD deficiency is made by a quantitative spectrophotometric analysis or, more commonly, by a rapid fluorescent spot test detecting the generation of NADPH from NADP. The test is positive if the blood spot fails to fluoresce under ultraviolet light. Newborn screening for G6PD deficiency is not performed routinely in the United States, although it is done in countries with high disease prevalence. The World Health Organization recommends screening all newborns in populations with a prevalence of 3 to 5 percent or more in males.”

Genetic Testing for von-Willebrand Disease

Centers for Disease Prevention and Control (CDC), via the National Heart Lung and Blood Institute, National Institutes of Health (NHLBI-NIH)

Guidelines for diagnosis and management of von Willebrand disease (VWD) were developed for practicing primary care and specialist clinicians—including family physicians, internists, obstetrician-gynecologists, pediatricians, and nurse-practitioners—as well as hematologists and laboratory medicine specialists, which included the following recommendations for the diagnosis of VWD, which notably do not include genetic testing:

“The following recommendations include specific clinical history, physical findings, laboratory assays, and diagnostic criteria that this Panel suggests will allow the most definitive diagnosis of VWD.

- Tests such as the bleeding time, PFA-100®, or other automated functional platelet assays have been used but there are conflicting data with regard to sensitivity and specificity for VWD. Therefore, the Panel believes current evidence does not support their routine use as screening tests for VWD.
- The Panel believes that platelet-based assays should be used for the ristocetin cofactor method.
- The Panel emphasizes the importance of the timing of the phlebotomy for assays, with the patient at his/her optimal baseline as far as possible. (For example, VWF levels may be elevated above baseline during the second and third trimesters of pregnancy or during estrogen replacement, during acute inflammation such as the perioperative period, during infections, and during acute stress.) The careful handling and processing of the sample is also critical, particularly if the sample will be sent out for testing at a distant location.”

Coding Implications

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from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

Reviews, Revisions, and Approvals	Revision Date	Approval Date
Policy developed.	02/22	02/22

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Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is

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consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of member/enrollees. This clinical policy is not intended to recommend treatment for member/enrollees. Member/enrollees should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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Note: For Medicaid member/enrollees, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Note: For Medicare member/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at <http://www.cms.gov> for additional information.

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