

# GENETIC TESTING: HEMATOLOGIC CONDITIONS (NON-CANCEROUS)

## OVERVIEW

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.

## POLICY REFERENCE TABLE

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

<a href="#">Coverage Criteria Sections</a>	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
<b><a href="#">Known Familial Variant Analysis for Hematologic Conditions (non-cancerous)</a></b>				
<a href="#">Known Familial Variant Analysis</a>	Targeted Mutation Analysis for a Known Familial Variant	81403		
<b><a href="#">Inherited Thrombophilia</a></b>				
<a href="#">Factor V Leiden (F5) and Prothrombin (F2) Variant Analysis for Inherited Thrombophilia</a>	F5 R506Q Targeted Mutation Analysis	81241	D68.51, D68.2, D68.59, Z86.2, I82.90	2, 3, 7, 8, 9, 15
	F2 G20210A Targeted Mutation Analysis	81240	D68.52, D68.2, R79.1, I82.409	
<b><a href="#">Hemoglobinopathies</a></b>				
<a href="#">HBA1/HBA2 and/or HBB Variant Analysis</a>	HBA1 Deletion/Duplication Analysis HBA2 Deletion/Duplication Analysis HBA1 Sequencing Analysis	81257, 81259, 81269, S3845, S3850	D56.0, D56.9, D53.9, R70.1, D56.3, D56.8, Z86.2	1, 4, 5, 6

	HBA2 Sequencing Analysis			
	HBB Sequencing Analysis HBB Deletion/Duplication Analysis HBB Targeted Mutation Analysis	81361, 81362, 81363, 81364, 81479, S3846	D57.00-D57.81 9, D56.1, D64.9, R53.83	
<b>Hemophilia</b>				
<a href="#">F8 and/or F9 Variant Analysis</a>	F8 Targeted Mutation Analysis F8 Deletion/Duplication Analysis F8 Sequencing Analysis F9 Targeted Mutation Analysis F9 Deletion/Duplication Analysis F9 Sequencing Analysis	81238, 81403, 81406, 81407, 81479	D66, I62.9, M25, N92.2, R04.0, R31	13, 14, 21
<b>Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency</b>				
<a href="#">G6PD Variant Analysis</a>	G6PD Targeted Mutation Analysis G6PD Sequencing Analysis	81247, 81248, 81249	D55.0	11, 12
<b>von Willebrand Disease</b>				
<a href="#">GP1BA and/or VWF Variant Analysis</a>	GP1BA Triple Exon Analysis VWF Triple Exon Analysis Von Willebrand Disease Genetic Analysis	81401, 81403, 81405, 81408, 81479	D68.0	19, 20
<b>Other Covered Hematologic Conditions (non-cancerous)</b>				
<a href="#">Other Covered Hematologic Conditions (non-cancerous)</a>	See list below	81400-81408		16, 17, 18

## OTHER RELATED POLICIES

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

- **Oncology: Molecular Analysis of Solid Tumors and Hematologic Malignancies** for coverage criteria related to exome and genome sequencing of solid tumors and hematologic malignancies.
- **Genetic Testing: Prenatal and Preconception Carrier Screening** for coverage criteria related to carrier screening in the prenatal, preimplantation, and preconception setting.

- **Genetic Testing: Prenatal Diagnosis (via amniocentesis, CVS, or PUBS) and Pregnancy Loss** for coverage related to prenatal and pregnancy loss diagnostic genetic testing for tests intended to diagnose genetic conditions following amniocentesis, chorionic villus sampling or pregnancy loss.
- **Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay** for coverage criteria related to diagnostic genetic testing for conditions affecting multiple organ systems.
- **Genetic Testing: Metabolic, Endocrine, and Mitochondrial Disorders** for coverage criteria related to genetic testing for *MTHFR*.
- **Genetic Testing: General Approach to Genetic Testing** for coverage criteria related to genetic testing for non-cancerous hematologic disorders that are not specifically discussed in this or another non-general policy.

## COVERAGE CRITERIA

### KNOWN FAMILIAL VARIANT ANALYSIS FOR HEMATOLOGIC CONDITIONS (NON-CANCEROUS)

- I. Targeted mutation analysis for a known familial variant (81403) for a non-cancerous hematologic condition is considered **medically necessary** when:
  - A. The member has a close relative<sup>1</sup> with a known pathogenic or likely pathogenic variant causing the condition.
- II. Targeted mutation analysis for a known familial variant (81403) for a non-cancerous hematologic condition is considered **investigational** for all other indications.

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## INHERITED THROMBOPHILIA

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

- I. *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 meets at least one of the following:
1. A first unprovoked venous thromboembolism (VTE) <50 years old, **OR**
  2. VTE at unusual sites (such as hepatic portal, mesenteric, and cerebral veins), **OR**
  3. Recurrent VTE, **OR**
  4. Personal history of VTE with:
    - a) two or more close relatives<sup>1</sup> with a history of VTE, **OR**
    - b) one first-degree<sup>1a</sup> relative with VTE at a young age, **OR**
  5. Low activated protein C (APC) resistance activity, **OR**
  6. Female under the age of 50 who smokes tobacco and has a history of acute myocardial infarction, **OR**
  7. The member has a first-degree<sup>1a</sup> sibling known to be homozygous for factor V Leiden or factor II c.\*97G>A, **OR**
  8. Asymptomatic pregnant female or female contemplating pregnancy, with a first-degree<sup>1a</sup> relative with unprovoked VTE or VTE provoked by pregnancy or contraceptive use, **OR**
  9. Pregnant female or female contemplating pregnancy or estrogen use who has a first-degree<sup>1a</sup> relative with:
    - a) a history of VTE, **AND**
    - b) is a known carrier for factor V Leiden and/or factor II c.97\*G>A variant, **OR**
  10. Pregnant female or female contemplating pregnancy with a previous non-estrogen-related VTE or VTE provoked by a minor risk factor.
- II. *F5* (81241) and *F2* (81240) variant analysis to confirm or establish a diagnosis of an inherited thrombophilia is considered **investigational** for all other indications.

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## HEMOGLOBINOPATHIES

### ***HBA1/HBA2* and/or *HBB* Variant Analysis**

- I. *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:
  - A. The member's hematologic screening results (e.g., MCV, MCH, CBC, hemoglobin electrophoresis, or dichlorophenol indophenol (DCIP)) are positive for a hemoglobinopathy, **OR**
  - B. The member'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. *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 **investigational** for all other indications.

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## HEMOPHILIA

### ***F8* and/or *F9* Variant Analysis**

- I. *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:
  - A. The member has any of the following clinical features of hemophilia:
    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),  
**OR**
- B. The following laboratory features:
1. Normal platelet count, **AND**
  2. Prolonged activated partial thromboplastin time (aPTT), **AND**
  3. Normal prothrombin time (PT), **OR**
- C. Both of the following:
1. The members biological sex is female, **AND**
  2. The member has a biological child with clinical or laboratory features of hemophilia A or B.
- D. *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 **investigational** for all other indications.

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## GLUCOSE-6-PHOSPHATE DEHYDROGENASE (G6PD) DEFICIENCY

### **G6PD Variant Analysis**

- I. *G6PD* variant analysis (81247, 81248, 81249) to confirm or establish a diagnosis\* of glucose-6-phosphate dehydrogenase deficiency is considered **investigational**.

\* 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.

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## VON-WILLEBRAND DISEASE

### ***GP1BA* and *VWF* Variant Analysis**

- I. *GP1BA* and/or *VWF* variant analysis (81401, 81403, 81405, 81408) to confirm or establish a diagnosis\* of von-Willebrand disease is considered **investigational**.

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

## OTHER COVERED HEMATOLOGIC CONDITIONS (NON-CANCEROUS)

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

- I. Genetic testing to establish or confirm one of the following hematologic conditions (non-cancerous) to guide management is considered **medically necessary** when the member 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. 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 *General Approach to Genetic Testing* (see policy for coverage 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.

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## 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

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## BACKGROUND AND RATIONALE

### Practice Guidelines and Position Statements

#### 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 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  $\alpha$ -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

<b>Society</b>	<b>Year</b>	<b>Recommendation</b>
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.”
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*

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.”

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