Concert Genetic Testing: Hematologic Conditions (Non-Cancerous)

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Date of Last Revision 01/25

Coding implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

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

Coding Implications

This clinical policy references Current Procedural Terminology (CPT®). CPT is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2023, American Medical Association. All rights reserved. CPT codes and CPT descriptions are 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 and may not support medical necessity. 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.

The tests, associated laboratories, CPT codes, and ICD codes contained within this document serve only as examples to help users navigate claims and corresponding criteria; as such, they are not comprehensive and are not a guarantee of coverage or non-coverage. Please see the Concert Platform for a comprehensive list of registered tests.

NOTE: Coverage is subject to each requested code's inclusion on the corresponding LDH fee schedule. Non-covered codes are denoted (*) and are reviewed for Medical Necessity for members under 21 years of age on a per case basis. The non-covered codes will only be denoted in the table below and not throughout the policy. Please only reference the policy reference table for covered and non-covered codes.

Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
Inherited Thrombophilia				
Factor V Leiden (*F5*) and Prothrombin (*F2*) Variant Analysis for Inherited Thrombophilia	Factor V (Leiden) Mutation Analysis (Quest Diagnostics)	81241	D68.51, D68.2, D68.59, R79.1, Z86.2, I82.90	1, 5
F5 (Factor V Leiden) Variant Analysis	Prothrombin (Factor II) 20210G>A Mutation Analysis (Quest Diagnostics)	81240*	D68.52, D68.2, D68.59, R79.1, Z86.2, I82.90	2, 3, 7, 8, 9, 10, 14
Hemoglobinopathies				
HBA1/*HBA2* and/or *HBB* Variant Analysis	Alpha Thalassemia Panel (Prevention Genetics, part of Exact Sciences)	81259*, 81269*	D56.0, D56.9, D53.9, R70.1, D56.3, D56.8, Z86.2	2, 3, 4, 6
	Alpha-Globin Common Mutation Analysis (Quest Diagnostics)	81257*		
	Beta Globin (HBB) Sequencing (ARUP Laboratories)	81364*	D57, D56.1, D64.9	
	Beta Globin Gene Dosage Analysis (Quest Diagnostics)	81363*		
Hemophilia				
Factor VIII (F8) and Factor IX (F9) Variant Analysis for Hemophilia A and B	Factor VIII (Hemophilia A) Genetic Analysis (Labcorp)	81403*, 81406*, 81407*	D66, I62.9, M25, N92.2, R04.0, R31	8, 9
	Factor IX (Hemophilia B) Genetic Analysis (Labcorp)	81238*	D67, I62.9, M25, N92.2, R04.0, R31	
Glucose-6-Phosphate Dehydrogenase (*G6PD*) Deficiency				
G6PD Variant Analysis	G6PD Targeted Variant - Single Test (GeneDx) G6PD Full Gene Sequencing and Deletion/Duplication (Invitae)	81247*, 81248*, 81249*, 81479	D55.0	7, 14
von Willebrand Disease				
VWF Variant Analysis	Von Willebrand Disease Gene Sequencing (Quest)	81408*, 81479	D68.0	10
Other Covered Hematologic Conditions (non-cancerous)				
Other Covered Hematologic	See list below	81400*, 81401*,		11, 12, 13

Conditions (non-cancerous)		81402*, 81403*, 81404*, 81405*, 81406*, 81407*, 81408*		

OTHER RELATED POLICIES

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

- ***Oncology: Molecular Analysis of Solid Tumors and Hematologic Malignancies*** for criteria related to exome and genome sequencing of solid tumors and hematologic malignancies.
- ***Genetic Testing: Prenatal and Preconception Carrier Screening*** for 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 criteria related to diagnostic genetic testing for conditions affecting multiple organ systems.
- ***Genetic Testing: Metabolic, Endocrine, and Mitochondrial Disorders*** for criteria related to genetic testing for *MTHFR*.
- ***Genetic Testing: General Approach to Genetic and Molecular Testing*** for criteria related to genetic testing for non-cancerous hematologic disorders that are not specifically discussed in this or another non-general policy, including known familial variant testing.

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CRITERIA

It is the policy of Louisiana Healthcare Connections that the specific genetic testing noted below is medically necessary when meeting the related criteria:

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 is considered **medically necessary** when:

A. The member/enrollee had a venous thromboembolism (VTE) that meets at least one of the following:

1. Provoked by a nonsurgical major transient risk factor, **OR**
2. Provoked by pregnancy or postpartum, **OR**
3. Provoked by combination oral contraceptive use, **OR**

B. The member/enrollee is planning to discontinue anticoagulation after venous thromboembolism (VTE), **AND**

1. The member/enrollee has a history of one of the following:

a) Cerebral venous thrombosis, **OR**

b) Splanchnic venous thrombosis, **OR**

C. The member/enrollee has a minor provoking risk factor for VTE (e.g. immobility, minor injury, illness, infection), **AND**

1. The member/enrollee has two first- or second-degree relatives with VTE, **OR**
2. The member/enrollee meets both of the following:

a) At least one of the relatives had VTE under age 50, **AND**

b) The relative's thrombophilia status is unknown, **OR**

D. The member/enrollee is a female planning a pregnancy, **AND**

1. Has a first- or second-degree relative who is known to be homozygous for factor V Leiden, **OR**
2. Has a first- or second-degree relative who is known to be a compound heterozygote for factor V Leiden and prothrombin (F2) mutation, **OR**

E. The member/enrollee is receiving systemic cancer treatment, **AND**

1. Does not have a personal history of VTE, **AND**
2. Has a first-degree relative with VTE.

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, including:

A. Fetal loss or adverse pregnancy outcomes (examples: placental abruption, fetal growth restriction, or preeclampsia).

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HEMOGLOBINOPATHIES

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

I. *HBA1*/*HBA2* variant analysis (81257, 81259, 81269) and/or *HBB* variant analysis (81363, 81364) to confirm or establish a diagnosis of a hemoglobinopathy (alpha-thalassemia, beta-thalassemia, or sickle cell disease) is considered **medically necessary** when:

A. The member/enrollee's hematologic screening results (examples: MCV, MCH, CBC, hemoglobin electrophoresis, or dichlorophenol indophenol (DCIP)) are positive for a hemoglobinopathy, **OR**

B. The member/enrollee's hematologic screening results (examples: MCV, MCH, CBC, hemoglobin electrophoresis, or dichlorophenol indophenol (DCIP)) do not conclusively diagnose or rule out a hemoglobinopathy.

II. *HBA1*/*HBA2* variant analysis (81257, 81259, 81269) and/or *HBB* variant analysis (81363, 81364) to confirm or establish a diagnosis of a hemoglobinopathy (alpha-thalassemia, beta-thalassemia, or sickle cell disease) is considered **investigational** for all other indications.

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HEMOPHILIA

Factor VIII (F8) and Factor IX (F9) Variant Analysis for Hemophilia A and B

I. *F8* variant analysis (81403, 81406, 81407) and/or *F9* variant analysis (81238) to confirm or establish a diagnosis of hemophilia A or B is considered **medically necessary** when:

A. The member/enrollee has any of the following clinical features of hemophilia:

1. Hemarthrosis (especially with mild or no antecedent trauma), **OR**
2. Deep-muscle hematomas, **OR**
3. Intracranial bleeding in the absence of major trauma, **OR**

4. Neonatal cephalohematoma or intracranial bleeding, **OR**
5. Prolonged oozing or renewed bleeding after initial bleeding stops following tooth extractions, mouth injury, or circumcision, **OR**
6. Prolonged, delayed bleeding, or poor wound healing following surgery or trauma, **OR**
7. Unexplained GI bleeding or hematuria, **OR**
8. Heavy or prolonged menstrual bleeding (especially with onset at menarche), **OR**
9. Prolonged nosebleeds, especially recurrent and bilateral, **OR**
10. Excessive bruising (especially with firm, subcutaneous hematomas), **OR**

B. The member/enrollee has the following laboratory features:

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

II. *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, 81479) 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

VWF Variant Analysis

I. *VWF* variant analysis (81408, 81479) 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.

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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 /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. 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 and Molecular 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.

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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.
2. **Nonsurgical transient risk factors** include confinement to bed in the hospital with acute illness for at least 3 days, or a combination of minor transient risk factors such as admission of less than 3 days with acute illness or confinement to bed outside of hospital for at least 3 days, or leg injury associated with decreased mobility for at least 3 days.

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BACKGROUND AND RATIONALE

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

American Society of Hematology (ASH)

Evidence based guidelines published in 2023 provide recommendations for testing for thrombophilia, including hereditary and acquired types. These recommendations are helpful to guide anticoagulation treatment for patients with a personal or family history of venous thromboembolism (VTE).

The panel provided conditional recommendations for thrombophilia testing in the following scenarios:

- patients with VTE associated with nonsurgical major transient or hormonal risk factors;
- patients with cerebral or splanchnic venous thrombosis, in settings where anticoagulation would otherwise be discontinued;
- individuals with a family history (first or second degree relative) of VTE when considering thromboprophylaxis for minor provoking risk factors and for guidance to avoid COCs/hormone replacement therapy;
- pregnant women with a family history (first or second degree relative) of high-risk thrombophilia types;
- patients with cancer receiving systemic therapy at low or intermediate risk of thrombosis and with a family history (first or second degree relative) of VTE.

The panel also strongly recommends against thrombophilia testing in the general population before starting combined oral contraceptives. (p. 7101)

American College of Obstetricians and Gynecologists (ACOG)

ACOG also published Practice Bulletin 197 (2018) on Inherited Thrombophilias in Pregnancy which states that "...screening for inherited thrombophilias is not recommended for women with a history of fetal loss or adverse pregnancy outcomes including abruption, preeclampsia, or fetal growth restriction because there is insufficient clinical evidence that antepartum prophylaxis with unfractionated heparin or low-molecular-weight-heparin prevents recurrence in these patients, and a causal association has not been established." (p. e23)

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

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online.

The recommended hemoglobinopathy evaluation testing for Alpha-Thalassemia, Beta-Thalassemia, and Sickle Cell Disease is as follows:

GeneReviews: Alpha-Thalassemia

Hemoglobin Bart hydrops fetalis (Hb Bart) syndrome, which is caused by deletion or inactivation of all four alpha globin genes, exhibits the following hematologic findings: severe macrocytic hypochromic anemia (in the absence of ABO or Rh blood group incompatibility), reticulocytosis (may be >60%), and peripheral blood smear with large, hypochromic red cells, severe anisopoikilocytosis, and numerous nucleated red cells. In addition, hemoglobin analysis will typically display decreased amounts or complete absence of hemoglobin A and increased amounts of Hb Bart.

Hemoglobin H disease (HbH disease), which is caused by deletion or inactivation of three alpha globin genes, exhibits the following hematologic findings: mild-to-moderate (rarely severe) microcytic hypochromic hemolytic anemia, moderate reticulocytosis (3%-6%), Peripheral blood smear with anisopoikilocytosis, and very rarely nucleated red blood cells, Red blood cell supravital stain showing HbH inclusions (β4 tetramers) in 5%-80% of erythrocytes following incubation of fresh blood smears with 1% brilliant cresyl blue for one to three hours. In addition, hemoglobin analysis will typically display the presence of 0.8%-40% HbH and 60%-90% hemoglobin A.

GeneReviews: Beta-Thalassemia

Beta-Thalassemia typically displays the following hematologic findings: microcytic hypochromic anemia, absence of iron deficiency, anisopoikilocytosis with nucleated red blood cells on peripheral blood smear, and decreased or complete absence of hemoglobin A (HbA) and increased hemoglobin A2 (HbA2) and often hemoglobin F (HbF) on hemoglobin analysis.

GeneReviews: Sickle Cell Disease

Laboratory features of sickle cell disease include: normocytic anemia; sickle cells, nucleated red blood cells, target cells, and other abnormal red blood cells on peripheral blood smear; Howell-Jolly bodies indicate hyposplenism; presence of hemoglobin S (HbS) on a hemoglobin assay (e.g., high-performance liquid chromatography [HPLC], isoelectric focusing, cellulose acetate electrophoresis, citrate agar electrophoresis) with an absence or diminished amount of HbA.

Viprakasit V, Ekwattanakit S. Clinical classification, screening and diagnosis for thalassemia

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

> "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." (p. 207)

Factor VIII (F8) and Factor IX (F9) Variant Analysis for Hemophilia A and B

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online. The recommended hemoglobinopathy evaluation testing for Hemophilia A and Hemophilia B is as follows:

GeneReviews: Hemophilia A and Hemophilia B

Individuals with Hemophilia A (factor VIII deficiency) or Hemophilia B (factor IX deficiency) can exhibit the following clinical symptoms:

- Hemarthrosis, especially with mild or no antecedent trauma
- Deep-muscle hematomas
- Intracranial bleeding in the absence of major trauma
- Neonatal cephalohematoma or intracranial bleeding
- Prolonged oozing or renewed bleeding after initial bleeding stops following tooth extractions, mouth injury, or circumcision
- Prolonged or delayed bleeding or poor wound healing following surgery or trauma
- Unexplained GI bleeding or hematuria
- Heavy menstrual bleeding, especially with onset at menarche
- Prolonged nosebleeds, especially recurrent and bilateral

- Excessive bruising, especially with firm, subcutaneous hematomas

The following are laboratory findings in individuals with Hemophilia A or Hemophilia B:

- Normal platelet count
- Prolonged activated partial thromboplastin time (aPTT) (Note: in mild hemophilia B, aPTT may be normal or mildly prolonged)
- Normal prothrombin time (PT)

G6PD Variant Analysis

American Academy of Family Physicians

Frank (2005) published guidelines in American Family Physician for evaluating individuals for *G6PD* deficiency, including specific laboratory tests which notably do not include genetic testing: "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." (p. 1278)

UpToDate: Diagnosis and management of glucose-6-phosphate dehydrogenase (G6PD) deficiency

Per this summary of G6PD diagnosis and management, the tests commonly used are semi-quantitative screening tests, some of which are done at the point-of-care. Positive screening tests should be followed up with a quantitative test that reports G6PD enzyme activity per gram of hemoglobin. If initial results are negative, testing should be repeated three months following resolution of the hemolytic episode. Confirmatory testing using molecular methods (DNA) is available; however, it is not used routinely and is not useful for those of African or Mediterranean ancestry.

VWF Variant Analysis

Centers for Disease Control and Prevention (CDC)

Guidelines for diagnosis and management of von Willebrand disease (VWD) were developed by the CDC 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 recommendations for laboratory tests to aid in the diagnosis of VWD, which notably do not include genetic testing.

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Reviews, Revisions, and Approvals	Revision Date	Approval Date	Effective Date
Converted corporate to local policy.	09/23	11/27/23	

Semi-annual review. Updated title to reflect V1.2024 version. Overview, coding, reference-table, background and references updated. Throughout policy: replaced "coverage criteria" with "criteria. For Policy Reference Table; under Hemoglobinopathies: added "(GeneDx)"; and added "HBA1 Single Gene…"; added "(ARUP Laboratories)"; under Hemophilia: remove "F8 Sequencing Analysis" and added "(GeneDx)…"; removed "Deletion/Duplication Analysis…"; added "Full Gene Sequencing…"; und Glucose-6-Phosphate Dehydrogenase…" removed "Mutation Analysis…"; and added "Variant-Single Test…"; under von Willebrand Disease: remove "Sequencing Analysis…" and added "Gene Sequencing…". For Other Related Policies: added "and Molecular". For Criteria; under Hemoglobinopathies: added "variant analysis"; under Von-Willebrand Disease: added "/or"; under Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency: added "and Molecular". For Background and Rationale; under Known Familial Variant Analysis for Hematologic Conditions (non-cancerous): changed "inheritance patterns" to "genetic testing".	12/23	2/27/24	
Semi-annual review. Updated title to reflect V2.2024 version. In Known Familial Variant Analysis for Hematologic Conditions (non-cancerous) criteria, moved criteria to policy "Genetic Testing: General Approach to Genetic and Molecular Testing" to consolidate criteria for known familial variant tests. Minor rewording for clarity throughout. Coding, reference-table, background and references updated.	06/24	9/17/24	10/17/24
Semi-annual review. Updated title to reflect V1.2025. G6PD Variant Analysis: Streamlined portions of Background and Rationale section for brevity; Updated access date for online reference. Factor VIII (F8) and Factor IX (F9) Variant Analysis for Hemophilia A and B: Criteria renamed to "Factor VIII (F8) and Factor IX (F9) Variant Analysis for Hemophilia A and B". VWF Variant Analysis: Updated example test in Policy Reference Table; Updated GeneReviews copyright dates in Reference list. Factor V Leiden (F5) and Prothrombin (F2) Variant Analysis for Inherited Thrombophilia: Updated References to the 2023 ASH guidelines. Hemoglobinopathies - HBA1/HBA2 and/or HBB Variant Analysis: Updated GeneReviews copyright dates in Reference list.	1/25	3/31/25	5/1/25

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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

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