BSC_CON_2.15	Genetic Testing: Hematologic Conditions (Non-Cancerous)		
Original Policy Date:	April 1, 2024	**Effective Date:**	April 1, 2024
Section:	2.0 Medicine	**Page:**	Page 1 of 17

Example Test Table

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

Policy Statement Locations	Example Tests, Labs	Common CPT Codes
Known Familial Variant Analysis for Hematologic Conditions (non-cancerous)		
Known Familial Variant Analysis for Hematologic Conditions (non-cancerous)	Targeted Mutation Analysis for a Known Familial Variant	81403, 81258, 81362
Inherited Thrombophilia		
Factor V Leiden (*F5*) and Prothrombin (*F2*) Variant Analysis for Inherited Thrombophilia	Factor V (Leiden) Mutation Analysis (Quest Diagnostics)	81241
	Prothrombin (Factor II) 20210G>A Mutation Analysis (Quest Diagnostics)	81240
Hemoglobinopathies		
HBA1/*HBA2* and/or *HBB* Variant Analysis	HBA1 Deletion/Duplication Analysis (GeneDx) HBA2 Deletion/Duplication Analysis (GeneDx) HBA1 Single Gene (Sequencing Only) (Fulgent Genetics) HBA2 Gene Sequencing (Fairview Diagnostic Laboratories)	81257, 81259, 81269, S3845, S3850
	HBB Sequencing Analysis (ARUP Laboratories) HBB Deletion/Duplication Analysis (GeneDx)	81361, 81363, 81364, S3846
Hemophilia		
F8 and/or *F9* Variant Analysis	F8 Deletion/Duplication Analysis (GeneDx) F8 Single Gene (Sequencing Only) (Fulgent Genetics)	81403, 81406, 81407
	F9 Full Gene Sequencing and Deletion/Duplication (Invitae)	81238, 81479
Glucose-6-Phosphate Dehydrogenase (*G6PD*) Deficiency		
G6PD Variant Analysis	G6PD Targeted Variant - Single Test (GeneDx) Carrier - G6PD Full Gene Sequencing and Deletion/Duplication (Invitae)	81247, 81248, 81249
von Willebrand Disease		
GP1BA and/or *VWF* Variant Analysis	GP1BA Gene Sequencing & Deletion/Duplication (Fairview Diagnostic Laboratories) VWF Targeted Variant - Single Test (GeneDx) Von Willebrand Disease (VWF) Sequencing (ARUP Laboratories)	81401, 81403, 81404, 81405, 81406, 81408, 81479
Other Covered Hematologic Conditions (non-cancerous)		
Other Covered Hematologic Conditions (non-cancerous)	See list in policy statement section	81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408

Policy Statement

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

I. Targeted mutation analysis for a known familial variant (81403, 81258, 81362) for a non-cancerous hematologic condition may be considered **medically necessary** when:
   A. The member has a close relative with a known pathogenic or likely pathogenic variant causing the condition.

II. Targeted mutation analysis for a known familial variant (81403, 81258, 81362) for a non-cancerous hematologic condition is considered **investigational** for all other indications.

Inherited Thrombophilia

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

III. *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) younger than 50 years old
      2. VTE at unusual sites (such as hepatic portal, mesenteric, and cerebral veins)
      3. Recurrent VTE
      4. Personal history of VTE with at least one of the following:
         a. Two or more family members with a history of VTE
         b. One first-degree relative with VTE at a young age
      5. Low activated protein C (APC) resistance activity
      6. The member is a female under the age of 50 who smokes tobacco and has a history of acute myocardial infarction
      7. The member has a first-degree relative known to be homozygous for factor V Leiden or factor II c.*97G>A
      8. The member is an asymptomatic pregnant female or female contemplating pregnancy, with a first-degree relative with unprovoked VTE or VTE provoked by pregnancy or contraceptive use
      9. The member is a pregnant female or female contemplating pregnancy or estrogen use who has a first-degree relative with **both** of the following:
         a. A history of VTE
         b. The member is a known carrier for factor V Leiden and/or factor II c.97*G>A variant
      10. The member is a pregnant female or female contemplating pregnancy with a previous non-estrogen-related VTE or VTE provoked by a minor risk factor.

IV. *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).

Hemoglobinopathies

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

V. *HBA1*/*HBA2* variant analysis (81257, 81259, 81269, S3845, S3850), and/or *HBB* variant analysis (81361, 81363, 81364, S3846) to confirm or establish a diagnosis of a hemoglobinopathy (alpha-thalassemia, beta-thalassemia, or sickle cell disease) may be considered **medically necessary** when **either** of the following criteria are met:
   A. The member's hematologic screening results (examples: MCV, MCH, CBC, hemoglobin electrophoresis, or dichlorophenol indophenol (DCIP)) are positive for a hemoglobinopathy

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

VI. *HBA1*/*HBA2* variant analysis (81257, 81259, 81269, S3845, S3850), and/or *HBB* variant analysis (81361, 81363, 81364, S3846) to confirm or establish a diagnosis of a hemoglobinopathy (alpha-thalassemia, beta-thalassemia, or sickle cell disease) is considered **investigational** for all other indications.

Hemophilia

F8 and/or *F9* Variant Analysis

VII. *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 **either** of the following criteria are met:
   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, 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. The member has **all** of the following laboratory features:
      1. Normal platelet count
      2. Prolonged activated partial thromboplastin time (aPTT)
      3. Normal prothrombin time (PT).

VIII. *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.

Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency

G6PD Variant Analysis

IX. *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.

Von-Willebrand Disease

GP1BA and/or *VWF* Variant Analysis

X. *GP1BA* and/or *VWF* variant analysis (81401, 81403, 81404, 81405, 81406, 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.

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.

XI. Genetic testing to establish or confirm one of the following hematologic conditions (non-cancerous) to guide management may be 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

XII. 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 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.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

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

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.

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. ***(to be published)***
- ***Genetic Testing: Metabolic, Endocrine, and Mitochondrial Disorders*** for coverage criteria related to genetic testing for *MTHFR*.
- ***Genetic Testing: General Approach to Genetic and Molecular 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.

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

- N/A

Rationale

Known Familial Variant Analysis for Hematologic Conditions (non-cancerous)
Genetic Support Foundation
The Genetic Support Foundation's Genetics 101 information on genetic testing says the following about testing for familial pathogenic variants:
Genetic testing for someone who may be at risk for an inherited disease is always easier if we know the specific genetic cause. Oftentimes, the best way to find the genetic cause is to start by testing someone in the family who is known or strongly suspected to have the disease. If their testing is positive, then we can say that we have found the familial pathogenic (harmful) variant. We can use this as a marker to test other members of the family to see who is also at risk.

Factor V Leiden (*F5*) and Prothrombin (*F2*) Variant Analysis for Inherited Thrombophilia
American College of Medical Genetics and Genomics (ACMG)
The American College of Medical Genetics and Genomics (Zhang, 2018) published updated technical standards for genetic testing for variants associated with VTE, with a focus on factor V Leiden and factor II. Testing is recommended for factor V Leiden and factor II c.*97G>A for the following indications:

1.) A first unprovoked VTE, especially <50 years old
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 family members with a history of VTE or (b) one first-degree relative with VTE at a young age

5.) Patients with low activated protein C (APC) resistance activity (p. 1492)

In addition, this testing "may be considered" for the following indications:

1.) Females under the age of 50 who smoke tobacco and have a history of acute myocardial infarction
2.) Siblings of individuals known to be homozygous for factor V Leiden or factor II c.*97G>A, because they have a 1 in 4 chance of being a homozygote
3.) Asymptomatic pregnant female or female contemplating pregnancy, with a first-degree relative with unprovoked VTE or VTE provoked by pregnancy or contraceptive use
4.) Pregnant female or female contemplating pregnancy or estrogen use who has a first-degree relative with a history of VTE and is a known carrier for factor V Leiden and/or factor II c.97*G>A variant
5.) Pregnant female or female contemplating pregnancy with a previous non-estrogen-related VTE or VTE provoked by a minor risk factor, because knowledge of the factor V Leiden or factor II c.*97G>A status may alter pregnancy-related thrombophylaxis (p. 1492-1493)

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).

Hemoglobinopathies - *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 of microcytic hypochromic anemia, anisopoikilocytosis with nucleated red blood cells on peripheral blood smear, and hemoglobin analysis that reveals decreased amounts or complete absence of hemoglobin A and increased amounts of hemoglobin F.

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)

Hemophilia - *F8* and/or *F9* 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 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
- Menorrhagia, 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)
- Normal prothrombin time (PT)

Glucose-6-Phosphate Dehydrogenase Deficiency - 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)"

von Willebrand Disease - *GP1BA* and/or *VWF* Variant Analysis
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 recommendations for laboratory tests to aid in the diagnosis of VWD, which notably do not include genetic testing.

References

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11. Genetic Support Foundation. Genetics 101 Genetic Testing: Familial Pathogenic Variant. Accessed 10/4/2022. https://geneticsupportfoundation.org/genetics-101/#
12. MedlinePlus [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: https://medlineplus.gov/genetics/.
13. Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1116/

14. Online Mendelian Inheritance in Man, OMIM. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD). World Wide Web URL: https://omim.org/

Documentation for Clinical Review

Please provide the following documentation:

- Name of the test being requested or the Concert Genetics GTU identifier. The Concert Genetics GTU can be found at https://app.concertgenetics.com
- CPT codes to be billed for the particular genetic test (GTU required for unlisted codes)
- History and physical and/or consultation notes including:
  - Clinical findings:
    - Signs/symptoms leading to a suspicion of genetic condition
    - Family history if applicable
  - Prior evaluation/treatment:
    - Previous test results (i.e., imagining, lab work, etc.) related to reason for genetic testing
    - Family member's genetic test result, if applicable
  - Rationale
    - Reason for performing test
    - How test result will impact clinical decision making

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	81238	F9 (coagulation factor IX) (e.g., hemophilia B), full gene sequence
	81240	F2 (prothrombin, coagulation factor II) (e.g., hereditary hypercoagulability) gene analysis, 20210G>A variant
	81241	F5 (coagulation factor V) (e.g., hereditary hypercoagulability) gene analysis, Leiden variant
	81247	G6PD (glucose-6-phosphate dehydrogenase) (e.g., hemolytic anemia, jaundice), gene analysis; common variant(s) (e.g., A, A-)
	81248	G6PD (glucose-6-phosphate dehydrogenase) (e.g., hemolytic anemia, jaundice), gene analysis; known familial variant(s)
	81249	G6PD (glucose-6-phosphate dehydrogenase) (e.g., hemolytic anemia, jaundice), gene analysis; full gene sequence
	81257	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (e.g., alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; common deletions or variant (e.g., Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, Constant Spring)

Type	Code	Description
	81258	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (e.g., alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; known familial variant
	81259	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (e.g., alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; full gene sequence
	81269	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (e.g., alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; duplication/deletion variants
	81361	HBB (hemoglobin, subunit beta) (e.g., sickle cell anemia, beta thalassemia, hemoglobinopathy); common variant(s) (e.g., HbS, HbC, HbE)
	81362	HBB (hemoglobin, subunit beta) (e.g., sickle cell anemia, beta thalassemia, hemoglobinopathy); known familial variant(s)
	81363	HBB (hemoglobin, subunit beta) (e.g., sickle cell anemia, beta thalassemia, hemoglobinopathy); duplication/deletion variant(s)
	81364	HBB (hemoglobin, subunit beta) (e.g., sickle cell anemia, beta thalassemia, hemoglobinopathy); full gene sequence
	81400	Molecular pathology procedure, Level 1 (e.g., identification of single germline variant [e.g., SNP] by techniques such as restriction enzyme digestion or melt curve analysis)
	81401	Molecular pathology procedure, Level 2 (e.g., 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
	81402	Molecular pathology procedure, Level 3 (e.g., >10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD])
	81403	Molecular pathology procedure, Level 4 (e.g., analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
	81404	Molecular pathology procedure, Level 5 (e.g., analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
	81405	Molecular pathology procedure, Level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
	81406	Molecular pathology procedure, Level 7 (e.g., analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons)
	81407	Molecular pathology procedure, Level 8 (e.g., analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform)
	81408	Molecular pathology procedure, Level 9 (e.g., analysis of >50 exons in a single gene by DNA sequence analysis)
	81479	Unlisted molecular pathology procedure
HCPCS	S3845	Genetic testing for alpha-thalassemia

Type	Code	Description
	S3846	Genetic testing for hemoglobin E beta-thalassemia
	S3850	Genetic testing for sickle cell anemia

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
04/01/2024	New policy.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	**AFTER**
New policy **Policy Statement:** N/A	**Known Familial Variant Analysis For Hematologic Conditions (Non-Cancerous)** I. Targeted mutation analysis for a known familial variant (81403, 81258, 81362) for a non-cancerous hematologic condition may be considered **medically necessary** when: A. The member has a close relative with a known pathogenic or likely pathogenic variant causing the condition. II. Targeted mutation analysis for a known familial variant (81403, 81258, 81362) for a non-cancerous hematologic condition is considered **investigational** for all other indications. **Inherited Thrombophilia** **Factor V Leiden (*F5*) and Prothrombin (*F2*) Variant Analysis for Inherited Thrombophilia** III. *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) younger than 50 years old 2. VTE at unusual sites (such as hepatic portal, mesenteric, and cerebral veins) 3. Recurrent VTE 4. Personal history of VTE with at least one of the following: a. Two or more family members with a history of VTE b. One first-degree relative with VTE at a young age 5. Low activated protein C (APC) resistance activity 6. The member is a female under the age of 50 who smokes tobacco and has a history of acute myocardial infarction 7. The member has a first-degree relative known to be homozygous for factor V Leiden or factor II c.*97G>A 8. The member is an asymptomatic pregnant female or female contemplating pregnancy, with a first-degree

POLICY STATEMENT	
BEFORE	**AFTER**
	relative with unprovoked VTE or VTE provoked by pregnancy or contraceptive use 9. The member is a pregnant female or female contemplating pregnancy or estrogen use who has a first-degree relative with **both** of the following: a. A history of VTE b. The member is a known carrier for factor V Leiden and/or factor II c.97*G>A variant 10. The member is a pregnant female or female contemplating pregnancy with a previous non-estrogen-related VTE or VTE provoked by a minor risk factor. IV. *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). **Hemoglobinopathies** ***HBA1*/*HBA2* and/or *HBB* Variant Analysis** V. *HBA1*/*HBA2* variant analysis (81257, 81259, 81269, S3845, S3850), and/or *HBB* variant analysis (81361, 81363, 81364, S3846) to confirm or establish a diagnosis of a hemoglobinopathy (alpha-thalassemia, beta-thalassemia, or sickle cell disease) may be considered **medically necessary** when **either** of the following criteria are met: A. The member's hematologic screening results (examples: MCV, MCH, CBC, hemoglobin electrophoresis, or dichlorophenol indophenol (DCIP)) are positive for a hemoglobinopathy B. The member's hematologic screening results (examples: MCV, MCH, CBC, hemoglobin electrophoresis, or dichlorophenol indophenol (DCIP)) do not conclusively diagnose or rule out a hemoglobinopathy. VI. *HBA1*/*HBA2* variant analysis (81257, 81259, 81269, S3845, S3850), and/or *HBB* variant analysis (81361, 81363, 81364, S3846) to confirm or establish a diagnosis of a hemoglobinopathy (alpha-thalassemia,

POLICY STATEMENT	
BEFORE	**AFTER**
	beta-thalassemia, or sickle cell disease) is considered **investigational** for all other indications. **Hemophilia** ***F8* and/or *F9* Variant Analysis** VII. *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 **either** of the following criteria are met: 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, 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. The member has **all** of the following laboratory features: 1. Normal platelet count 2. Prolonged activated partial thromboplastin time (aPTT) 3. Normal prothrombin time (PT). VIII. *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. **Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency**

POLICY STATEMENT	
BEFORE	**AFTER**
	***G6PD* Variant Analysis** IX. *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. **Von-Willebrand Disease** ***GP1BA* and/or *VWF* Variant Analysis** X. *GP1BA* and/or *VWF* variant analysis (81401, 81403, 81404, 81405, 81406, 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. **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. XI. Genetic testing to establish or confirm one of the following hematologic conditions (non-cancerous) to guide management may be 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

POLICY STATEMENT	
BEFORE	**AFTER**
	XII. 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 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.