Genetic and Coagulation Testing for Noncancer Blood Disorders

Humana

Medical Coverage Policy

Effective Date: 04/25/2024
Revision Date: 04/25/2024
Review Date: 04/25/2024
Policy Number: HUM-0525-018

Change Summary: Updated Description, Coverage Determinations, Coverage Limitations, Provider Claims Codes, References

Humana's documents are updated regularly online. When printed, the version of this document becomes uncontrolled. Do not rely on printed copies for the most up-to-date version. Refer to Medical and Pharmacy Coverage Policies to verify that this is the current version before utilizing.

Disclaimer

Description

Blood disorders can affect any of the three main components of blood including erythrocytes (red blood cells [RBCs]), leukocytes (white blood cells [WBCs]), thrombocytes (platelets) or tissues where these are formed (bone marrow, lymph nodes and spleen).

Coagulation (blood clotting) disorders are defects in the liver's ability to make sufficient amounts of proteins (eg, fibrinogen, prothrombin) needed to assist in the formation of blood clots and can result in hemorrhage (too little clotting) or thrombosis (too much clotting). Blood and coagulation disorders may be acquired (caused by disease or side effects of medication) or inherited (caused by genes).

Most bleeding and clotting disorders are caused by abnormalities in hemostasis (eg, dysfunction of platelets and/or clotting proteins). Less commonly, excessive bleeding or clotting can be caused by abnormalities in the fibrinolytic system (fibrinolysis).[70]

Atypical hemolytic uremic syndrome (aHUS) is a disorder that causes abnormal blood clots to form in small blood vessels in the kidneys or other parts of the body (thrombotic microangiopathy [TMA]). These clots can restrict or block blood flow causing hemolytic anemia, thrombocytopenia and kidney failure. aHUS can occur at any age and often results from a combination of acquired and inherited factors. *G6PD* gene testing has been proposed to detect pathogenic variants for the diagnoses of hemolytic anemia and jaundice which is associated with G6PD enzyme deficiency. **(Refer to Coverage Limitations section)**

Blood group antigens play a role in recognizing foreign cells in the bloodstream. If a blood type mismatch occurs during a blood transfusion it could lead to an immune response and possible illness. RBC antigen genotyping assays have been proposed as an alternative approach to determining compatibility of donated blood. Blood group genotyping purportedly overcomes blood grouping limitations by looking directly into the DNA sequence and thereby avoiding any donor cell or antibody interference. **(Refer to Coverage Limitations section)**

Bone marrow failure syndromes (BMFS) are rare diseases that occur in an individual who produces an insufficient amount of red blood cells, white blood cells or platelets and may be acquired or inherited. Inherited BMFS occurs from germline mutations that are passed down from parents. The majority are inherited in an autosomal recessive manner (eg, Fanconi anemia, Shwachman-Diamond syndrome, congenital amegakaryocytic thrombocytopenia, reticular dysgenesis) while a small subset is inherited in X-linked recessive (eg, dyskeratosis congenita) or autosomal dominant patterns (eg, Blackfan-Diamond anemia, reticular dysgenesis). Large mutigene panels have been proposed to diagnose these disorders. **(Refer to Coverage Limitations section)**

Complement hyperactivation, angiopathic thrombosis and protein-losing enteropathy (CHAPLE) syndrome is a rare inherited disorder of the immune system that is caused by variations of the complement regulator *CD55* gene, which can lead

to the complement system attacking the body's own cells. The disorder usually manifests in childhood and can be life-threatening.

Hemoglobinopathies are a group of inherited blood disorders that primarily affect RBCs causing abnormal production or structure of the hemoglobin molecule. They are inherited single-gene disorders and include sickle cell anemia, alpha- and beta-thalassemias.

Hereditary Thrombotic Thrombocytopenic Purpura (hTTP) is a rare autosomal recessive disorder caused by the absence of a functional protease (ADAMTS13) that processes von Willebrand factor multimers into smaller fragments. The multimers bind to platelets and initiate abnormal clotting, thrombosis and hemolysis throughout the body.

Neutropenia is a condition characterized by abnormally low levels of neutrophils, a type of white blood cell that is mainly produced in the bone marrow. Most causes of neutropenia are acquired (eg, autoimmune disorders, infection, side effects of medication/chemotherapy) with congenital neutropenia being less common.

Plasminogen activator inhibitor-1 (PAI-1) is an inhibitor of fibrinolysis, the clot dissolving portion of the coagulation process. PAI-1 is under investigation as a risk factor for conditions such as cardiovascular disease, thrombophilia and pregnancy-related complications. The PAI-1 test is an antibody-based enzyme assay. **(Refer to Coverage Limitations section)**

For information regarding **FVL, PAI-1, prothrombin genetic testing for cardiovascular disease**, please refer to Genetic Testing for Cardiac Conditions Medical Coverage Policy.

Sickle cell disease (SCD) is an autosomal recessive genetic condition that alters the shape and function of the hemoglobin molecule in RBCs. SCD is characterized by frequent and unpredictable vaso-occlusive complications (VOCs) that result from reduced blood flow in the microvasculature, including red cell stickiness and erythrocyte sickling. These processes lead to pain, chronic organ damage and decreased life expectancy. Flow-based adhesion and mechanical fragility assays are proposed to measure possible biomarkers associated with anemia/hemolysis, cellular adhesion, cellular aggregates, inflammation, coagulation, microparticles and

nitric oxide metabolism during a VOC state to help assess an individual's response to disease modifying therapy. **(Refer to Coverage Limitations section)**

Thrombocytopenia is a condition characterized by abnormally low levels of thrombocytes in the blood that can lead to hypocoagulation. Fetal and neonatal alloimmune thrombocytopenia (FNAIT) (fetomaternal alloimmune thrombocytopenia [FMAIT]) is the most common cause of severe thrombocytopenia in a fetus or newborn.[56] This occurs when inherited platelet antigens from the mother and father are incompatible, resulting in fetal platelet destruction. Maternal and paternal human platelet antigen (HPA) genotyping is commonly used to confirm a diagnosis. Heparin-induced thrombocytopenia (HIT) is a rare immune response to the drug heparin (a blood thinning medication) and is associated with arterial and venous thrombosis.

Thrombophilia (also known as hypercoagulability) is a disorder of blood coagulation that increases the risk for blood clots (thrombosis) in veins or arteries. Thrombophilia can be acquired or inherited. The most common acquired thrombophilias occur as a result of injury, surgery or a medical condition. The most common hereditary thrombophilias are factor V Leiden (FVL), due to a variant in the *F5* gene and prothrombin G20210A, as a result of a variant in the *F2* gene.

Von Willebrand disease (VWD) is the most common inherited blood clotting disorder and affects approximately 1 in 100 individuals. VWD is caused by deficient or defective plasma von Willebrand factor (VWF), a large multimeric glycoprotein that assists with primary hemostasis to prevent and stop bleeding. VWD is most commonly characterized by mucocutaneous (eg, epistaxis, genitourinary, gastrointestinal, gingival or petechiae) bleeding. The types of inherited VWD include type 1, type 2 (contains various subtypes), type 3 and platelet type. Acquired Von Willebrand syndrome (aVWS) is less common and may be associated with the use of extracorporeal membrane oxygenation (ECMO) or left ventricular assist devices (LVAD). Conditions such as aortic stenosis, autoimmune disorders (eg, antiphospholipid antibody syndrome, scleroderma and systemic lupus erythrematosus), congenital cardiac anomalies or myeloproliferative neoplasms may also contribute to aVWS.

For information regarding **genetic testing for myeloproliferative neoplasms (MPNs)**, please refer to Janus Kinase 2 (JAK2), Calreticulin (CALR) and

Myeloproliferative Leukemia (MPL) Variant Analysis and Genetic Testing for Diagnosis and Monitoring of Cancer Medical Coverage Policies.

For information regarding **genetic testing for the following**, please refer to Genetic Testing Medical Coverage Policy:

- DNA banking or preservation
- General population screening
- Individual 17 years of age or younger for adult-onset conditions
- Interpretation and reporting for molecular pathology procedure
- Polygenic risk score (PRS) and single nucleotide polymorphisms (SNPs)
- Repeat germline or somatic genetic testing
- Retrieved archival tissue

Humana recognizes that the field of genetic testing is rapidly changing and that other tests may become available.

Coverage Determination

Any state mandates for genetic testing take precedence over this medical coverage policy.

Genetic testing may be excluded by certificate. Please consult the member's individual certificate regarding Plan coverage.

Apply General Criteria for Genetic and Pharmacogenomics Tests when disease- or gene-specific criteria are not available on a medical coverage policy. For information regarding **General Criteria for Genetic and Pharmacogenomics Tests**, please refer to Genetic Testing Medical Coverage Policy.

Alpha Thalassemia (*HBA1* and *HBA2* Genes)
Humana members may be eligible under the Plan for ***HBA1/HBA2*** **gene testing** when the following criteria are met:

- Pre- and post-test genetic counseling; **AND**
    - Individual to be tested has a first-degree relative with confirmed diagnosis; **OR**

- Individual to be tested has equivocal or indeterminate diagnosis based on results of prior testing such as complete blood count (CBC) and hemoglobin analysis by qualitative/quantitative electrophoresis, high performance liquid chromatography (HPLC) or isoelectric focusing; **OR**

- To establish disease-causing variant in an individual with a confirmed diagnosis

Testing strategy:

1. Test for known familial variant (KFV) if known; **OR**

2. If KVF testing has not been performed, then targeted analysis for common deletions of *HBA1* and *HBA2* may be pursued:

   a. Perform sequence analysis of *HBA1* and *HBA2* if a common deletion of *HBA1/2* is not identified

   b. Deletion/duplication analysis of *HBA1, HBA2* and MCS-R2 for uncommon deletions may be performed next, if no pathogenic variant is identified with sequence analysis

Beta Thalassemia and Sickle Cell Disease (Anemia) (*HBB* Gene)

Humana members may be eligible under the Plan for ***HBB* gene testing** when the following criteria are met:

- Pre- and post-test genetic counseling; **AND**

  - Individual to be tested has a first-degree relative with confirmed diagnosis; **OR**

  - Individual to be tested has equivocal or indeterminate diagnosis based on results of prior testing such as complete blood count (CBC) and hemoglobin analysis by qualitative/quantitative electrophoresis, high performance liquid chromatography (HPLC) or isoelectric focusing; **OR**

  - To establish disease-causing variant in an individual with a confirmed diagnosis

Testing strategy:

1. Test for known familial variant (KFV) if known; **OR**

2. If KVF testing has not been performed, then Perform *HBB* gene sequence analysis

    a. Perform targeted deletion/duplication analysis of *HBB* gene if only 1 or no pathogenic variant is identified with sequence analysis

CD55-Deficient Protein-Losing Enteropathy (CHAPLE Disease) (*CD55*)

Humana members may be eligible under the Plan for ***CD55* gene testing for CD55-deficient protein-losing enteropathy (PLE) (CHAPLE disease)** (0182U) when the following criteria are met:

- Pre- and post-test counseling; **AND**
- Individual to be tested is 1 year of age or older; **AND**
- Clinical suspicion of PLE (eg, abdominal pain, nausea, vomiting, diarrhea, loss of appetite, weight loss, impaired growth, swelling, severe thrombotic vascular occlusions); **AND**
- Testing is performed to establish eligibility for treatment with pozelimab-bbfg (Veopoz)

Factor V Leiden (FVL) Thrombophilia (*F5* Gene)

Humana members may be eligible under the Plan for ***F5* gene testing for FVL thrombophilia** when the following criteria are met:

- Pre- and post-test genetic counseling; **AND**
- Abnormal activated protein C (APC) resistance assay result, unless the individual presents with the following[55]**:**

- Has a known presence of lupus anticoagulant (lupus antibody, LA, LAC, lupus inhibitor); **OR**
- Is receiving direct thrombin inhibitor therapy (eg, argatroban, dabigatran); **OR**
- Is receiving factor Xa inhibitor therapy (eg, apixaban, rivaroxaban);

AND ANY of the following:

- Asymptomatic female who is planning pregnancy or is currently pregnant and not taking anticoagulation therapy;

  AND EITHER of the following

  - First-degree relative with a history of high-risk thrombophilia (eg, antithrombin deficiency, double heterozygosity or homozygosity for FVL or prothrombin G20210A); **OR**
  - First-degree relative with venous thromboembolism (VTE) before age 50 years; **OR**

- First unprovoked (from an unknown cause) VTE at any age; **OR**
- Individual with a first VTE AND a first-degree relative with a VTE occurring before 50 years of age; **OR**
- Individual with history of recurrent VTE; **OR**
- Venous thrombosis at unusual sites (eg, cerebral, hepatic, mesenteric and portal veins); **OR**
- VTE associated with the use of oral contraceptives or hormone replacement therapy (HRT); **OR**
- VTE during pregnancy or the puerperium

Hereditary Thrombotic Thrombocytopenic Purpura (hTTP) (*ADAMTS13*)
Humana members may be eligible under the Plan for ***ADAMTS13* gene testing for the identification of biallelic pathogenic variants** when the following criteria are met:

- Pre- and post-test counseling; **AND**
- Clinical suspicion of hTTP (eg, severe neonatal hyperbilirubinemia, recurrent thrombocytopenia or transient neurologic symptoms or stroke in a child or young adult); **AND**
- ADAMTS13 activity is <10% of normal with absence of autoantibodies; **AND**
- Testing is performed to establish eligibility for treatment with *ADAMTS13*, recombinant-krhn (Adzynma)

Human Platelet Antigen HPA-1a/b – 6a/b, 9a/b, 15a/b Genotyping
Humana members may be eligible under the Plan for **HPA genotyping for FNAIT (FMAIT)** when the following criteria are met:

- Pre- and post-test genetic counseling; **AND**
  - Current or previous pregnancy with suspected or confirmed alloimmune thrombocytopenia; **OR**
  - Fetal or neonatal bleeding of unknown etiology (eg, intracranial hemorrhage, mucosal bleeding, petechiae); **OR**
  - Maternal serology positive for alloantibodies against fetal/neonatal platelet antigen; **OR**
  - Neonate with severe thrombocytopenia (eg, platelet count less than 50,000/µL); **OR**
  - Screening of an individual with a first-degree relative with alloimmune thrombocytopenia

Prothrombin G20210A Thrombophilia (*F2* Gene)

Humana members may be eligible under the Plan for ***F2* gene testing for prothrombin G20210A thrombophilia** when the following criteria are met:

- Pre- and post-test genetic counseling; **AND**
  - Asymptomatic female who is planning pregnancy or is currently pregnant and not taking anticoagulation therapy;

    AND EITHER of the following:
    - First-degree relative with a history of high-risk thrombophilia (eg, antithrombin deficiency, double heterozygosity or homozygosity for FVL or prothrombin G20210A); **OR**
    - First-degree relative with VTE before 50 years of age; **OR**
  - First unprovoked (eg, from an unknown cause) VTE at any age; **OR**
  - Individual with a first VTE **AND** a first-degree relative with a VTE occurring before 50 years of age; **OR**
  - Individual with history of recurrent VTE; **OR**
  - Venous thrombosis at unusual sites (eg, cerebral, hepatic, mesenteric and portal veins); **OR**
  - VTE associated with the use of oral contraceptives or hormone replacement therapy (HRT); **OR**
  - VTE during pregnancy or the puerperium

Coverage Limitations

Humana members may **NOT** be eligible under the Plan for the following **coagulation tests** for any indication:

- Versiti Heparin-Induced Thrombocytopenia Evaluation – PEA (0275U)
- Versiti VWF Collagen III Binding (0279U)
- Versiti VWF Collagen IV Binding (0280U)
- Versiti VWF Propeptide Antigen (0281U)
- Versiti VWD Type 2B Evaluation (0283U)
- Versiti VWD Type 2N Binding (0284U)

All indications are considered not medically necessary as defined in the member's individual certificate. Please refer to the member's individual certificate for the specific definition.

Humana members may **NOT** be eligible under the Plan for **flow-based adhesion or mechanical fragility assays (0121U, 0122U, 0123U, 0303U, 0304U and 0305U)** for any indication. This technology is considered experimental/investigational as it is not identified as widely used and generally accepted for the proposed use as reported in nationally recognized peer-reviewed medical literature published in the English language.

Humana members may **NOT** be eligible under the Plan for ***ADAMTS13* gene testing** for any indications other than those listed above. This is considered experimental/ investigational as it is not identified as widely used and generally accepted for any other proposed use as reported in nationally recognized peer-reviewed medical literature published in the English language.

Humana members may **NOT** be eligible under the Plan for ***CD55* gene testing** (0182U) for any indications other than those listed above. This is considered experimental/ investigational as it is not identified as widely used and generally accepted for any other proposed use as reported in nationally recognized peer-reviewed medical literature published in the English language.

Humana members may **NOT** be eligible under the Plan for ***G6PD* gene testing (81247, 81248 and 81249)** for any indication. This technology is considered experimental/investigational as it is not identified as widely used and generally accepted for the proposed use as reported in nationally recognized peer-reviewed medical literature published in the English language.

Humana members may **NOT** be eligible under the Plan for **genetic testing for HPA genotyping for FNAIT (FMAIT)** for any indications other than those listed above. This is considered experimental/investigational as it is not identified as widely used and generally accepted for any other proposed use as reported in nationally recognized peer-reviewed medical literature published in the English language.

Humana members may **NOT** be eligible under the Plan for **genetic testing for inherited hemoglobinopathies or thrombophilias** for any indications other than those listed above. This is considered experimental/investigational as it is not identified as widely used and generally accepted for any other proposed use as reported in nationally recognized peer-reviewed medical literature published in the English language.

Humana members may **NOT** be eligible under the Plan for **multigene panel testing for the diagnosis of BMFS (81441)**. This technology is considered experimental/ investigational as it is not identified as widely used and generally accepted for the proposed use as reported in nationally recognized peer-reviewed medical literature published in the English language.

Humana members may **NOT** be eligible under the Plan for **multigene panels** unless **ALL** genes in the panel meet disease- or gene-specific criteria (Refer to Coverage Determination section or Limitations section for single genes in a panel). Examples include, but may not be limited to:

- Versiti aHUS Genetic Evaluation (0268U)
- Versiti Autosomal Dominant Thrombocytopenia Panel (0269U)
- Versiti Coagulation Disorder Panel (0270U)
- Versiti Comprehensive Bleeding Disorder Panel (0272U)
- Versiti Comprehensive Platelet Disorder Panel (0274U)
- Versiti Congenital Neutropenia Panel (0271U)
- Versiti Fibrinolytic Disorder Panel (0273U)
- Versiti Inherited Thrombocytopenia Panel (0276U)
- Versiti Platelet Function Disorder Panel (0277U)
- Versiti Thrombosis Panel (0278U)

These are considered experimental/investigational as they are not identified as

widely used and generally accepted for the proposed uses as reported in nationally recognized peer-reviewed medical literature published in the English language.

Humana members may **NOT** be eligible under the Plan for **plasminogen activator inhibitor-1 (PAI-1) testing** for any indication including pregnancy complications and VTE. This is considered experimental/investigational as it is not identified as widely used and generally accepted for the proposed use as reported in nationally recognized peer-reviewed medical literature published in the English language.

Humana members may **NOT** be eligible under the Plan for the following **RBC antigen genotyping assays (eg, 0001U, 0084U, 0180U, 0181U, 0183U to 0201U, 0221U, 0222U, 0246U, 0282U)** for any indication. This technology is considered experimental/investigational as it is not identified as widely used and generally accepted for the proposed use as reported in nationally recognized peer-reviewed medical literature published in the English language.

Humana members may **NOT** be eligible under the Plan for **genetic testing for noncancer blood disorders** for any genes, indications or tests other than those listed above including:

- Individual to be tested has an affected first-, second- or third-degree relative with a negative genetic testing result for the associated condition
- KFV detection analysis using either of the following methods:
    - KFV analysis using a multigene panel that includes the KFV
    - Sequencing, deletion/duplication analysis or large genomic rearrangement analysis (conducted individually, as comprehensive testing or sequentially) without KFV results of a first, second- or third-degree relative

These are considered not medically necessary as defined in the member's individual certificate. Please refer to the member's individual certificate for the specific definition.

Background

Additional information about **noncancer blood disorders** may be found from the following websites:

- National Library of Medicine

Medical Alternatives

Alternatives to ***G6PD* gene testing** include, but may not be limited to, the following:

- G6PD enzyme testing

Alternatives to **RBC genotyping** include, but may not be limited to, the following:

- ABO blood group and Rh factor identification
- Antibody screening
- RBC phenotype and crossmatching

Alternatives to **whole blood flow adhesion and mechanical fragility assays** include, but may not be limited to, the following:

- Complete blood count
- Reticulocyte count
- Urinalysis

Physician consultation is advised to make an informed decision based on an individual's health needs.

Humana may offer a disease management program for this condition. **The member may call the number on his/her identification card to ask about our programs to help manage his/her care.**

Provider Claims Codes

Any CPT, HCPCS or ICD codes listed on this medical coverage policy are for informational purposes only. Do not rely on the accuracy and inclusion of specific codes. Inclusion of a code does not guarantee coverage and or reimbursement for a service or procedure.

CPT® Code(s)	Description	Comments
81105	Human Platelet Antigen 1 genotyping (HPA-1), ITGB3 (integrin, beta 3 [platelet glycoprotein IIIa], antigen CD61 [GPIIIa]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-1a/b (L33P)	
81106	Human Platelet Antigen 2 genotyping (HPA-2), GP1BA (glycoprotein Ib [platelet], alpha polypeptide [GPIba]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-2a/b (T145M)	
81107	Human Platelet Antigen 3 genotyping (HPA-3), ITGA2B (integrin, alpha 2b [platelet glycoprotein IIb of IIb/IIIa complex], antigen CD41 [GPIIb]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-3a/b (I843S)	
81108	Human Platelet Antigen 4 genotyping (HPA-4), ITGB3 (integrin, beta 3 [platelet glycoprotein IIIa], antigen CD61 [GPIIIa]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-4a/b (R143Q)	
81109	Human Platelet Antigen 5 genotyping (HPA-5), ITGA2 (integrin, alpha 2 [CD49B, alpha 2 subunit of VLA-2 receptor] [GPIa]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant (eg, HPA-5a/b (K505E))	
81110	Human Platelet Antigen 6 genotyping (HPA-6w), ITGB3 (integrin, beta 3 [platelet glycoprotein IIIa, antigen CD61] [GPIIIa]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-6a/b (R489Q)	

81111	Human Platelet Antigen 9 genotyping (HPA-9w), ITGA2B (integrin, alpha 2b [platelet glycoprotein IIb of IIb/IIIa complex, antigen CD41] [GPIIb]) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-9a/b (V837M)	
81112	Human Platelet Antigen 15 genotyping (HPA-15), CD109 (CD109 molecule) (eg, neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-15a/b (S682Y)	
81240	F2 (prothrombin, coagulation factor II) (eg, hereditary hypercoagulability) gene analysis, 20210G>A variant	
81241	F5 (coagulation factor V) (eg, hereditary hypercoagulability) gene analysis, Leiden variant	
81247	G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; common variant(s) (eg, A, A-)	**Not Covered**
81248	G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; known familial variant(s)	**Not Covered**
81249	G6PD (glucose-6-phosphate dehydrogenase) (eg, hemolytic anemia, jaundice), gene analysis; full gene sequence	**Not Covered**
81257	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; common deletions or variant (eg, Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, Constant Spring)	
81258	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; known familial variant	
81259	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; full gene sequence	
81269	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; duplication/deletion variants	

81361	HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); common variant(s) (eg, HbS, HbC, HbE)	
81362	HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); known familial variant(s)	
81363	HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); duplication/deletion variant(s)	
81364	HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); full gene sequence	
81441	Inherited bone marrow failure syndromes (IBMFS) (eg, Fanconi anemia, dyskeratosis congenita, Diamond-Blackfan anemia, Shwachman-Diamond syndrome, GATA2 deficiency syndrome, congenital amegakaryocytic thrombocytopenia) sequence analysis panel, must include sequencing of at least 30 genes, including BRCA2, BRIP1, DKC1, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, GATA1, GATA2, MPL, NHP2, NOP10, PALB2, RAD51C, RPL11, RPL35A, RPL5, RPS10, RPS19, RPS24, RPS26, RPS7, SBDS, TERT, and TINF2	**Not Covered** **New Code Effective 01/01/2023**
85415	Fibrinolytic factors and inhibitors; plasminogen activator	**Not Covered if used to report any test outlined in Coverage Limitations section**
86022	Antibody identification; platelet antibodies	
96040	Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family	
0001U	Red blood cell antigen typing, DNA, human erythrocyte antigen gene analysis of 35 antigens from 11 blood groups, utilizing whole blood, common RBC alleles reported	**Not Covered**
0084U	Red blood cell antigen typing, DNA, genotyping of 10 blood groups with phenotype prediction of 37 red blood cell antigens	**Not Covered**

0121U	Sickle cell disease, microfluidic flow adhesion (VCAM-1), whole blood	**Not Covered**
0122U	Sickle cell disease, microfluidic flow adhesion (P-Selectin), whole blood	**Not Covered**
0123U	Mechanical fragility, RBC, shear stress and spectral analysis profiling	**Not Covered**
0180U	Red cell antigen (ABO blood group) genotyping (ABO), gene analysis Sanger/chain termination/conventional sequencing, ABO (ABO, alpha 1-3-N-acetylgalactosaminyltransferase and alpha 1-3-galactosyltransferase) gene, including subtyping, 7 exons	**Not Covered**
0181U	Red cell antigen (Colton blood group) genotyping (CO), gene analysis, AQP1 (aquaporin 1 [Colton blood group]) exon 1	**Not Covered**
0182U	Red cell antigen (Cromer blood group) genotyping (CROM), gene analysis, CD55 (CD55 molecule [Cromer blood group]) exons 1-10	
0183U	Red cell antigen (Diego blood group) genotyping (DI), gene analysis, SLC4A1 (solute carrier family 4 member 1 [Diego blood group]) exon 19	**Not Covered**
0184U	Red cell antigen (Dombrock blood group) genotyping (DO), gene analysis, ART4 (ADP-ribosyltransferase 4 [Dombrock blood group]) exon 2	**Not Covered**
0185U	Red cell antigen (H blood group) genotyping (FUT1), gene analysis, FUT1 (fucosyltransferase 1 [H blood group]) exon 4	**Not Covered**
0186U	Red cell antigen (H blood group) genotyping (FUT2), gene analysis, FUT2 (fucosyltransferase 2) exon 2	**Not Covered**
0187U	Red cell antigen (Duffy blood group) genotyping (FY), gene analysis, ACKR1 (atypical chemokine receptor 1 [Duffy blood group]) exons 1-2	**Not Covered**

0188U	Red cell antigen (Gerbich blood group) genotyping (GE), gene analysis, GYPC (glycophorin C [Gerbich blood group]) exons 1-4	**Not Covered**
0189U	Red cell antigen (MNS blood group) genotyping (GYPA), gene analysis, GYPA (glycophorin A [MNS blood group]) introns 1, 5, exon 2	**Not Covered**
0190U	Red cell antigen (MNS blood group) genotyping (GYPB), gene analysis, GYPB (glycophorin B [MNS blood group]) introns 1, 5, pseudoexon 3	**Not Covered**
0191U	Red cell antigen (Indian blood group) genotyping (IN), gene analysis, CD44 (CD44 molecule [Indian blood group]) exons 2, 3, 6	**Not Covered**
0192U	Red cell antigen (Kidd blood group) genotyping (JK), gene analysis, SLC14A1 (solute carrier family 14 member 1 [Kidd blood group]) gene promoter, exon 9	**Not Covered**
0193U	Red cell antigen (JR blood group) genotyping (JR), gene analysis, ABCG2 (ATP binding cassette subfamily G member 2 [Junior blood group]) exons 2-26	**Not Covered**
0194U	Red cell antigen (Kell blood group) genotyping (KEL), gene analysis, KEL (Kell metallo-endopeptidase [Kell blood group]) exon 8	**Not Covered**
0195U	KLF1 (Kruppel-like factor 1), targeted sequencing (ie, exon 13)	**Not Covered**
0196U	Red cell antigen (Lutheran blood group) genotyping (LU), gene analysis, BCAM (basal cell adhesion molecule [Lutheran blood group]) exon 3	**Not Covered**
0197U	Red cell antigen (Landsteiner-Wiener blood group) genotyping (LW), gene analysis, ICAM4 (intercellular adhesion molecule 4 [Landsteiner-Wiener blood group]) exon 1	**Not Covered**
0198U	Red cell antigen (RH blood group) genotyping (RHD and RHCE), gene analysis Sanger/chain termination/conventional sequencing, RHD (Rh blood group D antigen) exons 1-10 and RHCE (Rh blood group CcEe antigens) exon 5	**Not Covered**

0199U	Red cell antigen (Scianna blood group) genotyping (SC), gene analysis, ERMAP (erythroblast membrane associated protein [Scianna blood group]) exons 4, 12	**Not Covered**
0200U	Red cell antigen (Kx blood group) genotyping (XK), gene analysis, XK (X-linked Kx blood group) exons 1-3	**Not Covered**
0201U	Red cell antigen (Yt blood group) genotyping (YT), gene analysis, ACHE (acetylcholinesterase [Cartwright blood group]) exon 2	**Not Covered**
0221U	Red cell antigen (ABO blood group) genotyping (ABO), gene analysis, next-generation sequencing, ABO (ABO, alpha 1-3-N-acetylgalactosaminyltransferase and alpha 1-3-galactosyltransferase) gene	**Not Covered**
0222U	Red cell antigen (RH blood group) genotyping (RHD and RHCE), gene analysis, next-generation sequencing, RH proximal promoter, exons 1-10, portions of introns 2-3	**Not Covered**
0246U	Red blood cell antigen typing, DNA, genotyping of at least 16 blood groups with phenotype prediction of at least 51 red blood cell antigens	**Not Covered**
0268U	Hematology (atypical hemolytic uremic syndrome [aHUS]), genomic sequence analysis of 15 genes, blood, buccal swab, or amniotic fluid	**Not Covered**
0269U	Hematology (autosomal dominant congenital thrombocytopenia), genomic sequence analysis of 14 genes, blood, buccal swab, or amniotic fluid	**Not Covered**
0270U	Hematology (congenital coagulation disorders), genomic sequence analysis of 20 genes, blood, buccal swab, or amniotic fluid	**Not Covered**
0271U	Hematology (congenital neutropenia), genomic sequence analysis of 23 genes, blood, buccal swab, or amniotic fluid	**Not Covered**
0272U	Hematology (genetic bleeding disorders), genomic sequence analysis of 51 genes, blood, buccal swab, or amniotic fluid, comprehensive	**Not Covered**

0273U	Hematology (genetic hyperfibrinolysis, delayed bleeding), genomic sequence analysis of 8 genes (F13A1, F13B, FGA, FGB, FGG, SERPINA1, SERPINE1, SERPINF2, PLAU), blood, buccal swab, or amniotic fluid	**Not Covered**
0274U	Hematology (genetic platelet disorders), genomic sequence analysis of 43 genes, blood, buccal swab, or amniotic fluid	**Not Covered**
0275U	Hematology (heparin-induced thrombocytopenia), platelet antibody reactivity by flow cytometry, serum	**Not Covered**
0276U	Hematology (inherited thrombocytopenia), genomic sequence analysis of 23 genes, blood, buccal swab, or amniotic fluid	**Not Covered**
0277U	Hematology (genetic platelet function disorder), genomic sequence analysis of 31 genes, blood, buccal swab, or amniotic fluid	**Not Covered**
0278U	Hematology (genetic thrombosis), genomic sequence analysis of 12 genes, blood, buccal swab, or amniotic fluid	**Not Covered**
0279U	Hematology (von Willebrand disease [VWD]), von Willebrand factor (VWF) and collagen III binding by enzyme-linked immunosorbent assays (ELISA), plasma, report of collagen III binding	**Not Covered**
0280U	Hematology (von Willebrand disease [VWD]), von Willebrand factor (VWF) and collagen IV binding by enzyme-linked immunosorbent assays (ELISA), plasma, report of collagen IV binding	**Not Covered**
0281U	Hematology (von Willebrand disease [VWD]), von Willebrand propeptide, enzyme-linked immunosorbent assays (ELISA), plasma, diagnostic report of von Willebrand factor (VWF) propeptide antigen level	**Not Covered**
0282U	Red blood cell antigen typing, DNA, genotyping of 12 blood group system genes to predict 44 red blood cell antigen phenotypes	**Not Covered**
0283U	von Willebrand factor (VWF), type 2B, platelet-binding evaluation, radioimmunoassay, plasma	**Not Covered**

0284U	von Willebrand factor (VWF), type 2N, factor VIII and VWF binding evaluation, enzyme-linked immunosorbent assays (ELISA), plasma	**Not Covered**
0303U	Hematology, red blood cell (RBC) adhesion to endothelial/subendothelial adhesion molecules, functional assessment, whole blood, with algorithmic analysis and result reported as an RBC adhesion index; hypoxic	**Not Covered**
0304U	Hematology, red blood cell (RBC) adhesion to endothelial/subendothelial adhesion molecules, functional assessment, whole blood, with algorithmic analysis and result reported as an RBC adhesion index; normoxic	**Not Covered**
0305U	Hematology, red blood cell (RBC) functionality and deformity as a function of shear stress, whole blood, reported as a maximum elongation index	**Not Covered**
CPT® Category III Code(s)	**Description**	**Comments**
No code(s) identified		
HCPCS Code(s)	**Description**	**Comments**
S0265	Genetic counseling, under physician supervision, each 15 minutes	

References

1. American College of Medical Genetics and Genomics (ACMG). Venous thromboembolism laboratory testing (factor V Leiden and factor II c.*97G>A), 2018 update: a technical standard of the American College of Medical Genetics and Genomics (ACMG). https://www.acmg.net. Published December 2018.

2. American College of Obstetricians and Gynecologists (ACOG). Practice Bulletin. Hemoglobinopathies in pregnancy. https://www.acog.org. Published January 2007. Updated 2021.

3. American College of Obstetricians and Gynecologists (ACOG). Practice Bulletin. Inherited thrombophilias in pregnancy. https://www.acog.org. Published July 2018. Updated 2022.

4. American College of Obstetricians and Gynecologists (ACOG). Practice Bulletin. Prevention of Rh D alloimmunization. https://www.acog.org. Published August 2017. Updated 2021.

5. American College of Obstetricians and Gynecologists (ACOG). Practice Bulletin. Thrombocytopenia in pregnancy. https://www.acog.org. Published March 2019. Updated 2022.

6. ClinicalKey. Clinical Overview. Sickle cell disease. https://www.clinicalkey.com. Updated June 22, 2023.

7. ClinicalKey. Clinical Overview. Thalassemia. https://www.clinicalkey.com. Updated April 13, 2023.

8. ECRI Institute. ECRIgene Genetic Test Hotline Response. Genetic testing for atypical hemolytic uremic syndrome. https://www.ecri.org. Published December 2018.

9. ECRI Institute. Genetic Test Assessment. ID CORE XT genotyping test (Progenika Biopharma S.A., a Grifols Co.) for assessing blood donor-recipient compatibility. https://www.ecri.org. Published July 2020.

10. Fasano RM, Chou ST. Red blood cell antigen genotyping for sickle cell disease, thalassemia, and other transfusion complications. *Transfus Med Rev*. 2016;30(4):197-201.

11. Hayes, Inc. Genetic Test Evaluation (GTE) Clinical Utility Report. Genetic testing for common forms of hereditary thrombophilia in pediatric patients with unprovoked venous thromboembolism. https://evidence.hayesinc.com. Published August 1, 2019. Updated June 21, 2022.

12. Hayes, Inc. Genetic Test Evaluation (GTE) Clinical Utility Report. Genetic testing for factor V Leiden in women with unexplained recurrent pregnancy loss. https://evidence.hayesinc.com. Published December 18, 2018. Updated September 22, 2021.

13. Hayes, Inc. Genetic Test Evaluation (GTE) Clinical Utility Report (ARCHIVED). Genetic testing for common forms of hereditary thrombophilia in adults with unprovoked venous thromboembolism. https://evidence.hayesinc.com. Published May 21, 2019. Updated June 21, 2022.

14. Hayes, Inc. Genetic Test Evaluation (GTE) Report (ARCHIVED). Alpha thalassemia. https://evidence.hayesinc.com. Published February 5, 2015.

15. Hayes, Inc. Genetic Test Evaluation (GTE) Report (ARCHIVED). Factor V (F5) HR2 haplotype testing for hypercoagulability. https://evidence.hayesinc.com. Published April 18, 2012. Updated March 17, 2015.

16. Hayes, Inc. Genetic Test Evaluation (GTE) Report (ARCHIVED). Prothrombin G20210A for risk assessment for venous thromboembolism (VTE) or obstetric complications. https://evidence.hayesinc.com. Published October 2, 2008. Updated October 17, 2012.

17. Hayes, Inc. Genetic Test Evaluation (GTE) Report (ARCHIVED). von Willebrand factor (VWF) gene testing for von Willebrand disease (VWD). https://evidence.hayesinc.com. Published November 29, 2011. Updated December 2, 2014.

18. Hayes, Inc. Genetic Test Evaluation (GTE) Synopsis (ARCHIVED). Beta thalassemia. https://evidence.hayesinc.com. Published December 16, 2011.

19. Hayes, Inc. Genetic Test Evaluation (GTE) Synopsis (ARCHIVED). Sickle cell disease. https://evidence.hayesinc.com. Published December 19, 2011.

20. Johnson N, Kohr B, VanCott E. Advances in laboratory testing for thrombophilia. *Am. J. Hematol*. 2012;87:S108–S112.

21. Lane WJ, Westhoff CM, Gleadall NS, et al. Automated typing of red blood cell and platelet antigens: a whole-genome sequencing study. *Lancet Haematol*. 2018;5(6):241–251. https://www.ncbi.nlm.nih.gov/pmc.

22. MCG Health. Alpha thalassemia – HBA1 and HBA2 genes. 27th edition. https://humana.access.mcg.com/index.

23. MCG Health. Beta thalassemia – HBB gene. 27th edition. https://humana.access.mcg.com/index.

24. MCG Health. Factor V Leiden thrombophilia – F5 gene. 27th edition. https://humana.access.mcg.com/index.

25. MCG Health. Fanconi Anemia - FANC Genes and Gene Panel Testing. 27th edition. https://humana.access.mcg.com/index.

26. MCG Health. Fetal and neonatal alloimmune thrombocytopenia – human platelet antigen (HPA) genotyping. 27th edition. https://humana.access.mcg.com/index.

27. MCG Health. Hemoglobin C and E – HBB Gene. 27th edition. https://humana.access.mcg.com/index.

28. MCG Health. Prothrombin thrombophilia – F2 gene. 27th edition. https://humana.access.mcg.com/index.

29. MCG Health. Sickle cell disease – HBB gene. 27th edition. https://humana.access.mcg.com/index.

30. MCG Health. Von Willebrand disease – VWF gene. 27th edition. https://humana.access.mcg.com/index.

31. National Center for Biotechnology Information (NCBI). Genetic Testing Registry. Alpha-thalassemia. https://www.ncbi.nlm.nih.gov. Published November 1, 2005. Updated October 1, 2020.

32. National Center for Biotechnology Information (NCBI). Genetic Testing Registry. Beta-thalassemia. https://www.ncbi.nlm.nih.gov. Published September 28, 2000. Updated February 4, 2021.

33. National Center for Biotechnology Information (NCBI). Genetic Testing Registry. Factor V Leiden thrombophilia. https://www.ncbi.nlm.nih.gov. Published May 14, 1999. Updated January 4, 2018.

34. National Center for Biotechnology Information (NCBI). Genetic Testing Registry. Genetic atypical hemolytic-uremic syndrome. https://www.ncbi.nlm.nih.gov. Published November 16, 2007. Updated September 23, 2021.

35. National Center for Biotechnology Information (NCBI). Genetic Testing Registry. Prothrombin thrombophilia. https://www.ncbi.nlm.nih.gov. Published July 25, 2006. Updated February 4, 2021.

36. National Center for Biotechnology Information (NCBI). Genetic Testing Registry. Sickle cell disease. https://www.ncbi.nlm.nih.gov. Published September 15, 2003. Updated November 17, 2022.

37. National Center for Biotechnology Information (NCBI). Genetic Testing Registry. von Willebrand disease. https://www.ncbi.nlm.nih.gov. Published June 4, 2009. Updated April 29, 2022.

38. UpToDate, Inc. Acquired von Willebrand syndrome. https://www.uptodate.com. Updated June2023. Accessed July 9, 2023.

39. UpToDate, Inc. Acute vaso-occlusive pain management in sickle cell disease. https://www.uptodate.com. Updated June 2023. Accessed July 9, 2023.

40. UpToDate, Inc. Antithrombin deficiency. https://www.uptodate.com. Updated June 2023. Accessed July 9, 2023.

41. UpToDate, Inc. Clinical presentation and diagnosis of heparin-induced thrombocytopenia. https://www.uptodate.com. Updated June 2023. Accessed July 9, 2023.

42. UpToDate, Inc. Clinical presentation and diagnosis of von Willebrand disease. https://www.uptodate.com. Updated June 2023. Accessed July 9, 2023.

43. UpToDate, Inc. Diagnosis and management of glucose-6-phosphate dehydrogenase (G6PD) deficiency. https://www.uptodate.com. Updated June 2023. Accessed July 9, 2023.

44. UpToDate, Inc. Diagnosis of sickle cell disorders. https://www.uptodate.com. Updated June 2023. Accessed July 9, 2023.

45. UpToDate, Inc. Diagnosis of thalassemia (adults and children). https://www.uptodate.com. Updated June 2023. Accessed July 29, 2023.

46. UpToDate, Inc. Disorders of fibrinogen. https://www.uptodate.com. Updated June 2023. Accessed July 9, 2023.

47. UpToDate, Inc. Evaluating adult patients with established venous thromboembolism for acquired and inherited risk factors. https://www.uptodate.com. Updated June 2023.

48. UpToDate, Inc. Factor V Leiden and activated protein C resistance. https://www.uptodate.com. Updated June 2023.

49. UpToDate, Inc. Fetal and neonatal alloimmune thrombocytopenia: parental evaluation and pregnancy management. https://www.uptodate.com. Updated June 2023.

58. UpToDate, Inc. Genetics and pathophysiology of glucose-6-phosphate dehydrogenase (G6PD) deficiency. https://www.uptodate.com. Updated June 2023.

59. UpToDate, Inc. Heart failure in children: management. https://www.uptodate.com. Updated March 2024.

60. UpToDate, Inc. Hereditary thrombotic thrombocytopenic purpura (hTTP). https://www.uptodate.com. Updated March 2024.

50. UpToDate, Inc. Inherited thrombophilias in pregnancy. https://www.uptodate.com. Updated June 2023. Accessed July 9, 2023.

51. UpToDate, Inc. Methods for hemoglobin analysis and hemoglobinopathy testing. https://www.uptodate.com. Updated June 2023. Accessed July 11, 2023.

52. UpToDate, Inc. Molecular genetics of the thalassemia syndromes. https://www.uptodate.com. Updated June 2023. Accessed July 11, 2023.

53. UpToDate, Inc. Overview of the causes of venous thrombosis. https://www.uptodate.com. Updated June 2023. Accessed July 11, 2023.

54. UpToDate, Inc. Overview of the clinical manifestations of sickle cell disease. https://www.uptodate.com. Updated June 2023. Accessed July 11, 2023.

55. UpToDate, Inc. Pathophysiology of sickle cell disease. https://www.uptodate.com. Updated June 2023. Accessed July 11, 2023.

56. UpToDate, Inc. Pretransfusion testing for red blood cell transfusion. https://www.uptodate.com. Updated June 2023. Accessed July 11, 2023.

57. UpToDate, Inc. Prothrombin G20210A. https://www.uptodate.com. Updated June 2023. Accessed July 11, 2023.

58. UpToDate, Inc. Rare inherited coagulation disorders. https://www.uptodate.com. Updated June 2023. Accessed July 11, 2023.

59. UpToDate, Inc. Red blood cell antigens and antibodies. https://www.uptodate.com. Updated June 2023. Accessed July 11,2023.

60. UpToDate, Inc. Red blood cell transfusion in sickle cell disease: indications and transfusion techniques. https://www.uptodate.com. Updated June 2023. Accessed July 11, 2023.

61. UpToDate, Inc. Screening for inherited thrombophilia in asymptomatic adults. https://www.uptodate.com. Updated June 2023. Accessed July 11, 2023.

62. UpToDate, Inc. Thrombophilia testing in children and adolescents. https://www.uptodate.com. Updated June 2023. Accessed July 11, 2023.

63. UpToDate, Inc. Thrombotic and hemorrhagic disorders due to abnormal fibrinolysis. https://www.uptodate.com. Updated June 2023. Accessed July 11, 2023.

64. US Food & Drug Administration (FDA). Summary of safety and effectiveness data: ID CoreXT. https://www.fda.gov. Published October 11, 2018. Accessed August 2, 2022.

65. US Food & Drug Administration (FDA). Summary of safety and effectiveness data: PreciseType HEA. https://www.fda.gov. Published March 18, 2014. Accessed August 2, 2022.

66. White J, Lancelot M, Sarnaik S, Hines P. Increased erythrocyte adhesion to VCAM-1 during pulsatile flow: application of a microfluidic flow adhesion bioassay. *Clin Hemorheol Microcirc.* 2015;60(2):201-213. https://www.ncbi.nlm.nih.gov/pmc. Accessed July 9, 2023.

Appendix A

Pre- and Post-Test Genetic Counseling Criteria

Pre- and post-test genetic counseling performed by any of the following qualified medical professionals
Genetic counselor who is board-certified or board-eligible by the American Board of Medical Genetics and Genomics (ABMGG) or American Board of Genetic Counseling, Inc (ABGC) and is not employed by a commercial genetic testing laboratory; **OR**
Genetic clinical nurse (GCN) or advanced practice nurse in genetics (APNG) who is credentialed by the Genetic Nursing Credentialing Commission (GNCC) or the American of Nurses Credentialing Center (ANCC) and is not employed by a commercial genetic testing laboratory; **OR**
Medical geneticist who is board-certified or board-eligible by ABMGG; **OR**
Treating physician who has evaluated the individual to be tested and has completed a family history of three generations

Appendix B

Family Relationships

Degree of Relationship	Definition
First-degree	Child, full-sibling, parent
Second-degree	Aunt, uncle, grandchild, grandparent, nephew, niece, half-sibling
Third-degree	First cousin, great aunt, great-uncle, great-grandchild, great-grandparent, half-aunt, half-uncle