Revision log
Coding Implications

CONCERT GENETICS GENETIC TESTING: HEMATOLOGIC CONDITIONS (NON-CANCEROUS)

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. 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 and associated laboratories and CPT 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 Genetics Platform for a comprehensive list of registered tests.

Coverage 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
	Prothrombin (Factor II) 20210G>A Mutation Analysis (Quest Diagnostics)	81240	D68.52, D68.2, D68.59, R79.1, Z86.2, I82.90	
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				
F8 and/or *F9* Variant Analysis	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 Genetic Analysis (Labcorp)	81408, 81479	D68.0	10
Other Covered Hematologic Conditions (non-cancerous)				
Other Covered Hematologic Conditions (non-cancerous)	See list below	81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408		11, 12, 13

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.

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CRITERIA

It is the policy of health plans affiliated with Centene Corporation® 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 may be considered **medically necessary** when:

A. The member/enrollee meets at least one of the following:

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

9. The member/enrollee has a female reproductive system and is pregnant or contemplating pregnancy or estrogen use who has a first-degree relative with both of the following:

    a) A history of VTE, **AND**

    b) The member/enrollee is a known carrier for factor V Leiden and/or factor II c.97*G>A variant, **OR**

10. The member/enrollee has a female reproductive system and is pregnant or contemplating pregnancy with a previous non-estrogen-related VTE or VTE provoked by a minor risk factor.

II. *F5* (81241) and *F2* (81240) variant analysis to confirm or establish a diagnosis of an inherited thrombophilia is considered **investigational** for all other indications, 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

F8 and/or *F9* Variant Analysis

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 following laboratory features:

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

C. *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

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BACKGROUND AND RATIONALE

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.) Those with a female reproductive system 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.) Those with a female reproductive system who are asymptomatic and pregnant or contemplating pregnancy, with a first-degree relative with unprovoked VTE or VTE provoked by pregnancy or contraceptive use
4.) Those with a female reproductive system who are pregnant or 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.) Those with a female reproductive system who are pregnant or 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: 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)

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
- 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)

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)"

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, and quantitative tests that report G6PD enzyme activity per gram of hemoglobin. False-negative results may occur in some individuals with acute hemolysis because the most severely G6PD-deficient cells have been destroyed. In those situations, quantitative testing should be repeated three months after the hemolytic episode has resolved. DNA testing is available; however, it is not used routinely. Testing for pathogenic *G6PD* variants is not particularly useful in the assessment of G6PD-deficient individuals of African or Mediterranean background.

von Willebrand Disease - *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
Policy developed.	03/23	03/23
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: removed "F8 Sequencing Analysis" and added "(GeneDx)…"; removed "Deletion/Duplication Analysis…"; added "Full Gene Sequencing…"; under Glucose-6-Phosphate Dehydrogenase…" removed "Mutation Analysis…"; and added "Variant-Single Test…"; under von Willebrand Disease: removed "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".	10/23	10/23
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.	04/24	04/24

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Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

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

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

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

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

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