

Clinical Policy: Genetic Testing Gastroenterologic Disorders (non-cancerous)

Reference Number: CP.MP.221

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[Coding Implications](#)

[Revision Log](#)

See [Important Reminder](#) at the end of this policy for important regulatory and legal information.

Description

Genetic testing for gastroenterologic (non-cancerous) disorders may be used to confirm a diagnosis in a patient who has signs and/or symptoms of a specific gastroenterologic disorder. Confirming the diagnosis may alter aspects of management and may eliminate the need for further diagnostic workup. This document addresses genetic testing for common gastroenterologic (non-cancerous) conditions.

Genetic counseling is recommended for patients who are at risk for inherited disorders and who are interested in undergoing genetic testing. Interpreting the results of genetic tests and understanding risk factors can be challenging and genetic counseling helps in the understanding the potential impacts of genetic testing, including possible effects the test results could have on the individual or their family members. Genetic counseling may alter the utilization of genetic testing substantially and has been shown to reduce inappropriate testing and should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

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

CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
81403	Targeted Mutation Analysis for a Known Familial Variant	Known Familial Variant Analysis	N/A
81370, 81375, 81376, 81377, 81382, 81383	HLA-DQ Genotyping (ARUP Laboratories) Celiac Disease HLA Typing (Johns Hopkins Medical Institutions - Pathology Laboratory)	HLA-DQ Variant Analysis	K90.0, R10.0-R10.13, R10.3-R10.829, R10.84-R10.9
81256, 81479	HFE Sequencing Analysis	HFE Sequencing and/or Deletion/Duplication Analysis	E83.110, E83.118, E83.119, R79.0, E83.19, R16.0
81479	MCM6 Targeted Mutation Analysis	MCM6 Targeted Variant Analysis	E73.1

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CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
81401, 81404, 81405, 81479	Pancreatitis Panel (CFTR, CTRC, PRSS1, SPINK1) Sequencing (ARUP Laboratories) PRSS1 Targeted Mutation Analysis Test (Prevention Genetics) CTRC Sequencing Analysis SPINK1 Sequencing Analysis	Hereditary Pancreatitis Multigene Panel	K85.0-K85.92, K86.1, Z83.79
81479, 82397, 83520, 86140, 88346, 88350, 81499	Prometheus IBD sgi Diagnostic (Prometheus Laboratories)	Inflammatory Bowel Disease/Crohn’s Disease Diagnostic Algorithmic Tests	K50-K52
86255, 86256, 86671, 81499	Inflammatory Bowel Disease Panel (Children’s Hospital of Philadelphia)	Inflammatory Bowel Disease/Crohn’s Disease Diagnostic Algorithmic Tests	K50-K52
0203U	PredictSURE IBD (KSL Diagnostics)	Inflammatory Bowel Disease/Crohn’s Disease Prognostic Algorithmic Tests	K50-K52
83516, 86671, 81499	Crohn’s Disease Prognostic Panel (ARUP Laboratories)	Inflammatory Bowel Disease/Crohn’s Disease Prognostic Algorithmic Tests	K50-K52
81401, 83520, 86021, 86255, 81499	Prometheus Crohn’s Prognostic Panel (Prometheus Laboratories)	Inflammatory Bowel Disease/Crohn’s Disease Prognostic Algorithmic Tests	K50-K52
81479	Monogenic Inflammatory Bowel Disease Panel (Invitae) Infantile Enterocolitis and Inflammatory Bowel Disease	Hereditary Inflammatory Bowel Disease/Crohn’s Disease Panel Tests	K50-K52

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CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
	Monogenic (CGC Genetics USA) Very Early Onset Inflammatory Bowel Genomic Panel (Children’s Hospital of Philadelphia) Early Onset Inflammatory Bowel Disease (EGL Genetics)		
0002M	ASH FibroSURE (LabCorp)	Test Specific Gastroenterologic Disorders Tests	N/A
0003M	NASH FibroSURE (LabCorp)	Test Specific Gastroenterologic Disorders Tests	N/A
0114U	EsoGuard™ (Lucid Diagnostics)	Test Specific Gastroenterologic Disorders Tests	N/A

This policy document provides criteria for Genetic Testing for Gastroenterologic Conditions (non-cancerous). Please refer to:

- **CP.MP.225 Genetic Testing: Hereditary Cancer Susceptibility Syndromes** for criteria related to germline testing for hereditary cancer syndromes, including Lynch/HNPCC syndrome.
- **CP.MP.234 Genetic Testing: Prenatal and Preconception Carrier Screening** for criteria related to carrier screening in the prenatal, preimplantation, and preconception setting.
- **CP.MP.235 Genetic Testing: Prenatal Diagnosis (via amniocentesis, CVS, or PUBS) and Pregnancy Loss** for related to prenatal and pregnancy loss diagnostic genetic testing for tests intended to diagnose genetic conditions following amniocentesis, chorionic villus sampling or pregnancy loss.
- **CP.MP.230 Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay** for criteria related to diagnostic genetic testing for conditions affecting multiple organ systems.
- **CP.MP.229 Genetic Testing: Metabolic, Endocrine, and Mitochondrial Disorders** for criteria related to genetic testing for MTHFR.

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- **CP.MP.222 Genetic Testing: General Approach to Genetic Testing** for criteria related to genetic testing for any non-cancerous GI disorders that is not specifically discussed in this or another non-general policy.

Policy/Criteria

Known Familial Variant Analysis for Gastroenterologic Disorders

- I. It is the policy of health plans affiliated with Centene Corporation® that targeted mutation analysis for a known familial variant (81403) for a gastroenterologic disorder is considered **medically necessary** when:
 - A. The member/enrollee has a [close relative](#)¹ with a known pathogenic or likely pathogenic variant causing the condition.
- II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support targeted mutation analysis for a known familial variant (81403) for a gastroenterologic disorder for all other indications.

Celiac Disease

HLA-DQ Genotyping Analysis

- I. It is the policy of health plans affiliated with Centene Corporation® that *HLA-DQ2* and *HLA-DQ8* variant analysis (81370, 81375, 81376, 81377, 81382, 81383) to rule out celiac disease is considered **medically necessary** when meeting either of the following:
 - A. The member/enrollee meets both of the following:
 1. The member/enrollee has negative serologic and histologic testing,
 2. The member/enrollee has signs, symptoms, and or risk factors that indicate at least moderate to high risk of celiac disease (e.g., chronic diarrhea/steatorrhea with unintended weight loss, a first or second degree relative with celiac disease, type 1 DM, autoimmune thyroiditis, Down syndrome, Turner syndrome, pulmonary hemosiderosis),
 - B. The member/enrollee/enrollee has discordant serologic and histologic (biopsy) findings.
- II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support *HLA-DQ2* and *HLA-DQ8* variant analysis (81370, 81375, 81376, 81377, 81382, 81383) to rule out celiac disease for all other indications.

Hereditary Hemochromatosis

HFE Sequencing and/or Deletion/Duplication Analysis

- I. It is the policy of health plans affiliated with Centene Corporation® that *HFE* sequencing and/or deletion/duplication analysis (81256, 81479) to establish a diagnosis of hereditary hemochromatosis is considered **medically necessary** when:

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- A. The member/enrollee has abnormal serum iron indices, defined as transferrin saturation greater than or equal to 45% and/or elevated ferritin, indicating iron overload.
- II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support *HFE* sequencing and/or deletion/duplication analysis (81256, 81479) to screen for hereditary hemochromatosis in the general population.
- III. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support *HFE* sequencing and/or deletion/duplication analysis (81256, 81479) to establish a diagnosis of hereditary hemochromatosis for all other indications

Lactase Insufficiency

MCM6 Variant Analysis

- I. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support *MCM6* variant analysis (81479) for the prediction of lactase insufficiency.

Hereditary Pancreatitis

Hereditary Pancreatitis Multigene Panel

- I. It is the policy of health plans affiliated with Centene Corporation® that hereditary pancreatitis multigene panel analysis (81401, 81404, 81405, 81479) to establish a diagnosis of hereditary pancreatitis is considered **medically necessary** when meeting both of the following:
 - A. The member/enrollee meets at least one of the following:
 - 1. The member/enrollee has a [first^{1a}- or second-degree^{1b}](#) relative with pancreatitis,
 - 2. The member/enrollee is age 18 years or younger and has had an unexplained, documented episode of acute pancreatitis,
 - 3. The member/enrollee has had recurrent (i.e., two or more separate, documented episodes with hyper-amylasemia) attacks of acute pancreatitis for which there is no explanation (anatomical anomalies, ampullary or main pancreatic strictures, trauma, viral infection, gallstones, alcohol, drugs, hyperlipidemia, etc.),
 - 4. The member/enrollee has unexplained (i.e., idiopathic) chronic pancreatitis,
 - B. The panel includes, at a minimum, the following genes: *PRSSI*, *SPINK*.
- II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support hereditary pancreatitis multigene panel analysis (81401, 81404, 81405, 81479) to establish a diagnosis of hereditary pancreatitis for all other indications.

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Inflammatory Bowel Disease

Inflammatory Bowel Disease/Crohn's Disease Diagnostic Algorithmic Tests

- I. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support inflammatory bowel disease diagnostic algorithmic tests (81479, 82397, 83520, 86140, 86255, 86256, 86651, 88346, 88350, 81499).

Inflammatory Bowel Disease/Crohn's Disease Prognostic Algorithmic Tests

- I. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support inflammatory bowel disease prognostic algorithmic tests (0203U, 81401, 83516, 83520, 86021, 86255, 86671, 81499).

Hereditary Inflammatory Bowel Disease/Crohn's Disease Panel Tests

- I. It is the policy of health plans affiliated with Centene Corporation® that genetic testing for inflammatory bowel disease, including Crohn's disease via a multigene panel is considered **medically necessary** to confirm a diagnosis and/or determine appropriate treatment when meeting any of the following:
 - A. Patient has very early onset of symptoms before age 2 years,
 - B. Patient is a child or adolescent with aggressive, refractory or unusual IBD presentation,
 - C. Patient is a child or adolescent with IBD symptoms and with a family history of IBD or immunodeficiency in multiple family member/enrollee.
- II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support genetic testing for inflammatory bowel disease, including Crohn's disease, via a multigene panel for all other indications.

Test-Specific Gastroenterologic Disorders Tests

- I. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support the use of these specific gastroenterologic disorders tests:
 - A. ASH FibroSURE (0002M)
 - B. NASH FibroSURE (0003M)
 - C. EsoGuard™ (0114U)

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

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- c. **Third-degree relatives** are great grandparents, great aunts, great uncles, great grandchildren, and first cousins

Background

Genetic Testing for Celiac Disease

American College of Gastroenterology

The guidelines from the American College of Gastroenterology (2013) addressing the diagnosis and management of celiac disease (CD) stated the following on human leukocyte antigen (HLA) gene testing:

1. HLA-DQ2/DQ8 testing should not be used routinely in the initial diagnosis of CD [celiac disease] (Strong recommendation, moderate level of evidence).
2. HLA-DQ2/DQ8 genotyping testing should be used to effectively rule out the disease in selected clinical situations (Strong recommendation, moderate level of evidence).
3. Examples of such clinical situations include but are not limited to:
 - a. Equivocal small-bowel histological finding (Marsh I-II) in seronegative patients
 - b. Evaluation of patients on a gluten-free diet in whom no testing for CD was done before gluten-free diet
 - c. Patients with discrepant celiac-specific serology and histology
 - d. Patients with suspicion of refractory CD where the original diagnosis of celiac remains in question.

American College of Gastroenterology published guidelines (2018) addressing the management of Crohn's disease in adults state that genetic and routine serologic testing is not indicated to establish the diagnosis of Crohn's disease.

American Gastroenterological Association Institute

The American Gastroenterological Association Institute (2006) issued a position statement on the diagnosis and management of CD. Regarding serologic testing, the Institute concluded that, in the primary care setting, the transglutaminase immunoglobulin (Ig) A antibody test is the most efficient single serologic test for diagnosing CD.5, The guidelines indicated that the antiendomysial antibodies IgA test is more time-consuming and operator dependent than the tissue transglutaminase (tTG). If IgA deficiency is strongly suspected, testing with IgG anti endomysial antibody (EMA) and/or tTG IgG antibody test is recommended. If serologic test results are negative and CD is still strongly suspected, providers can test for the presence of the disease-associated HLA alleles and, if present, perform a small intestinal mucosal biopsy. Alternatively, if signs and symptoms suggest that small intestinal biopsy is appropriate, patients can proceed to biopsy without testing for HLA alleles.

U.S. Preventive Services Task Force

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The US Preventative Service Task Force (2017) released guidelines on screening adults and children for CD. These guidelines reviewed the use of tTG IgA testing followed by an intestinal biopsy to screen asymptomatic patients. Genotype testing was not discussed. The overall conclusion of this review was that the current balance of evidence was insufficient to assess benefits and harms resulting from screening for CD.

Genetic Testing for Hereditary Hemochromatosis

American College of Gastroenterology

In 2019, practice guidelines from the American College of Gastroenterology made the following statement on genetic testing for hereditary hemochromatosis:

"We recommend that family members, particularly first-degree relatives, of patients diagnosed with HH should be screened for HH (strong recommendation, moderate quality of evidence)."

Genetic Testing for Hereditary Pancreatitis

American College of Gastroenterology

In 2013, the American College of Gastroenterology guidelines on management of acute pancreatitis included the following statement: "Genetic testing may be considered in young patients (<30 years old) if no cause [of acute pancreatitis] is evident, and a family history of pancreatic disease is present (conditional recommendation, low quality of evidence).

In 2015, the American College of Gastroenterology Clinical Guideline: Genetic Testing and Management of Hereditary Gastrointestinal Cancer Syndromes recommended genetic testing of patients with suspected familial pancreatic cancer to include analysis of BRCA1/2, CDKN2A, PALB2, and ATM. Evaluation for Peutz-Jeghers Syndrome, Lynch Syndrome, and HP-associated genes should be considered if personal and/or family history criteria are met for the syndrome.

American Pancreatic Association

In 2014, the American Pancreatic Association published Practice Guidelines in Chronic Pancreatitis: Evidence-Based Report on Diagnostic Guidelines. A classification guideline for the etiology of chronic pancreatitis (CP) includes genetic mutations in PRSS1, CFTR, SPINK1, and others.

American Society of Clinical Oncology

In 2018, the American Society of Clinical Oncology (ASCO) published "Evaluating Susceptibility to Pancreatic Cancer: ASCO Provisional Clinical Opinion". The ASCO reported that cancer-unaffected individuals should be offered genetic risk evaluation if they are members of families with an identified pathogenic cancer susceptibility gene variant, from families that meet criteria for genetic evaluation for known hereditary syndromes that are linked to pancreatic cancer, and from families that meet criteria for familial pancreatic cancer. ASCO further considered what surveillance strategies should be used for individuals with a predisposition to pancreatic ductal adenocarcinoma to screen for pancreatic and other cancers. Surveillance can be considered for individuals who are first-degree relatives of individuals with familial pancreatic cancer and/or individuals with a family history of pancreatic cancer who carry a pathogenic germline variant in genes associated with predisposition to pancreatic cancer.

Genetic Testing for Inflammatory Bowel Disease / Crohn's Disease Diagnostic Algorithmic Tests

Concert Genetics Technical Assessment 2021

This review focused on peer-reviewed, published evidence of the clinical utility of Prometheus IBD sgi Diagnostic through November 9, 2021. PubMed and ECRI Guidelines Trust searches were performed. Search terms included Prometheus ibd sgi Diagnostic, and diagnosis inflammatory bowel disease serology genetic inflammation. References were also identified from the performing laboratory's website. A total of 45 abstracts from these sources were reviewed, and 13 full text publications were evaluated. At the present time, the Prometheus IBD sgi Diagnostic panel and similar tests have not been adequately shown in peer-reviewed publications to effectively result in improved health outcomes compared to the current standard of care.

Genetic Testing for Inflammatory Bowel Disease / Crohn's Disease Prognostic Algorithmic Tests

Concert Genetics Technical Assessment 2021

This review focused on peer-reviewed, published evidence of the clinical utility of prognostic tests for inflammatory bowel diseases through November 16, 2021. PubMed and ECRI Guidelines Trust searches were performed. Search terms included PredictSURE IBD, Prometheus, Crohn's disease prognostic, and biomarkers in ulcerative colitis/Crohn's disease. References were also identified from the performing laboratory's website. A total of 57 of abstracts were reviewed, with 13 full text publications selected for investigation. At the present time, prognostic serology testing for IBD has not been adequately shown in peer-reviewed publications to effectively result in improved health outcomes compared to the current standard of care.

Genetic Testing for Hereditary Inflammatory Bowel Disease / Crohn's Disease Panel Tests

UpToDate

Clinical features that raise suspicion for monogenic IBD include

- Young age of onset (eg, younger than six years, particularly younger than age two years)
- Family history of IBD and/or immunodeficiency in multiple family members, particularly with male predominance, or consanguinity
- Recurrent infections or unexplained fever
- Associated features of autoimmunity (eg, arthritis, primary sclerosing cholangitis, anemia, or endocrine dysfunction)
- Very severe IBD and/or resistance to conventional therapies for IBD
- Symptoms or signs suggesting hemophagocytic lymphohistiocytosis (hepatomegaly, fever, cytopenias, high ferritin)
- Lesions of the skin, nails, or hair
- Current or past history of cancer in the patient

Infants or young children presenting with these features warrant careful evaluation for monogenic IBD and consultation with an immunologist

European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHN)

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Summary of clinical features that should prompt considering a monogenic inflammatory bowel disease workup (Red flag signs)

Age of inflammatory bowel disease (IBD) presentation

- <2 years IBD symptom onset
- <6 years IBD symptom onset in particular when other red flag signs are present

Family history

- Affected family members with a suspected monogenic disorder
- Consanguinity
- Multiple family members with early-onset IBD

Comorbidity and extraintestinal manifestations are particularly relevant for monogenic IBD diagnostic considerations when rare or atypical for patient age irrespective of organ manifestation.

- Recurrent severe infections or atypical infections consistent with diagnostic criteria of a primary immunodeficiency
- Hemophagocytic lymphohistiocytosis
- Autoimmune features in particular features of Immunodysregulation polyendocrinopathy enteropathy X-linked syndrome
- Malignancies
- Multiple intestinal atresias

British Society of Gastroenterology

We suggest that genetic testing for monogenic disorders should be considered in adolescents and young adults who have had early onset (before 5 years of age) or particularly aggressive, refractory or unusual IBD presentations.

European Crohn’s and Colitis Organization (ECCO) and ESPGHN

1. In infants younger than 2 years, allergic colitis, immunological disorders and monogenic forms of colitis should be excluded.
2. Unusual disease evolution, history of recurrent infections, HLH, and non-response to multiple IBD medications may indicate an underlying genetic defect which should prompt genetic and/or immunological analyses at any age during childhood.

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 2021, 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.

Reviews, Revisions, and Approvals	Revision Date	Approval Date
Policy developed.	02/22	02/22

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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;

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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 members/enrollees. This clinical policy is not intended to recommend treatment for members/enrollees. Members/enrollees should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members/enrollees and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members/enrollees and their representatives agree to be bound by such terms and conditions by providing services to members/enrollees and/or submitting claims for payment for such services.

Note: For Medicaid members/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 members/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, 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.

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