Genetic Testing for Lactase Insufficiency

Policy # 00370
Original Effective Date: 07/17/2013
Current Effective Date: 08/10/2020

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of targeted MCM6 -13910C>T variant analysis for the prediction of lactase insufficiency to be **investigational.***

Policy Guidelines

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology-"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"-to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence

	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Background/Overview

Lactase

The predominant carbohydrate in milk is the disaccharide, lactose, comprising the simple sugars, glucose and galactose. The brush-border enzyme, lactase (also called lactase-phlorizin hydrolase), hydrolyzes lactose into its monosaccharide components, which are absorbable by the intestinal mucosa. Except in rare instances of congenital hypolactasia, most infants can produce lactase, and enzyme levels are highest at birth. Sometime after weaning in most children, there is a decrease in lactase production through a multifactorial process that is regulated at the gene transcription level.

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The decrease in lactase level varies significantly by ethnic group both in terms of the lowest level of lactase and time from weaning necessary to reach the nadir of lactase activity. By 2 to 12 years of age, 2 groups emerge: a group with insufficient levels of lactase activity (primary hypolactasia or lactase nonpersistence) and a group that retains the infant level of lactase activity through adulthood (lactase persistence). Ethnic groups with the highest prevalences of lactase insufficiency are Asian, Native Americans, and blacks, with the lowest prevalences in people of northern European origin (see Table 1).

Table 1. Prevalence of Lactase Insufficiency by Ethnicity

Populations	Percent Lactase Insufficient,[a] %
Northern Europeans	2-15
American whites	6-22
Central Europeans	9-23
Northern Indians	20-30
Southern Indians	60-70
Hispanics	50-80
Ashkenazi Jews	60-80
Blacks	60-80
American Indians	80-100
Asians	95-100

Adapted from Sahi (1994).
[a] Identified through hydrogen breath test or lactose tolerance blood test.

Several terms are used to describe lactose malabsorption:lactase insufficiency, lactose malabsorption, and lactose intolerance. We discuss each below.

Lactase Insufficiency
Lactase insufficiency (lactase non persistence or primary hypolactasia) indicates that lactase activity is a fraction of the original infantile level. Direct measurement of lactase activity is tested biochemically through duodenal biopsy. Lactase insufficiency is highly correlated with the C/C genotype at -13910 in the lactase promoter region. In adults homozygous for the lactase persistence genotype (T/T), lactase levels are approximately 10 times higher than in those who are homozygous lactase insufficient (C/C); heterozygous persons (C/T) have intermediate lactase activity levels. In

heterozygous people, symptoms of lactose intolerance may appear if the quantity of ingested lactose exceeds the maximum digestible by the reduced level of lactase.

Lactose Malabsorption
Lactose malabsorption indicates that a large portion of lactose cannot be absorbed in the small bowel and is delivered to the colon. Malabsorption is tested by hydrogen breath test (HBT) or lactose tolerance blood test.

Lactose Intolerance
Lactose intolerance indicates that lactose malabsorption causes gastrointestinal symptoms. There is no genetic test for lactose intolerance; demonstration of lactose intolerance requires patients to self-report symptoms after lactose ingestion. Diagnosis of lactose intolerance is highly susceptible to the placebo effect, and studies should conduct a blinded lactose challenge with an indistinguishable placebo. A meta-analysis by Jellema et al (2010) has indicated that no specific patient complaint could predict lactose malabsorption; for common lactose intolerance symptoms, sensitivity and specificity ranged from 0% to 90% and 18% to 96%, respectively. Similarly, patient self-reported milk intolerance was inaccurate for predicting lactose malabsorption, with sensitivity and specificity ranging from 30% to 70% and 25% to 87%, respectively.

Table 2. Symptoms of Lactose Intolerance

Symptoms	Percent of Total Patients Who Experience Symptoms, %
Gut-related symptoms	
Abdominal pain	100
Gut distention	100
Borborygmi (stomach rumbling)	100
Flatulence	100
Diarrhea	70
Nausea	78
Vomiting	78
Constipation	30
Systemic symptoms	
Headache and light headedness	86

Loss of concentration and poor short-term memory	82
Muscle pain	71
Joint pain and/or swelling	71
Long-term fatigue	63
Allergy (eczema, pruritus, rhinitis, sinusitis, asthma)	40
Mouth ulcers	30
Heart arrhythmia	24
Increased frequency of micturition	<20
Sore throat	<20

Adapted from Matthews et al (2005).

Symptoms

Lactase insufficiency is common, occurring in approximately 70% of persons after weaning. Lactase insufficiency results in lactose malabsorption, which may lead to symptoms of lactose intolerance such as abdominal pain, bloating, diarrhea, and increased flatulence, caused by bacterial fermentation of undigested lactose in the colon. However, demonstration of lactose malabsorption does not necessarily indicate that a person will be symptomatic. Factors that determine whether a person with lactose malabsorption will develop symptoms include the dose of lactose ingested; residual intestinal lactase activity; ingestion of food along with lactose; the ability of the colonic flora to ferment lactose; and individual sensitivity to the products of lactose fermentation. Because of these factors, the number of persons reporting symptoms of lactose intolerance is likely only a portion of those who are lactase insufficient. Also, lactose malabsorption may be secondary (secondary hypolactasia) to acquired conditions, such as small bowel bacterial overgrowth; infectious enteritis; mucosal damage due to celiac disease; inflammatory bowel disease; antibiotics; gastrointestinal surgery; short bowel syndrome; radiation enteritis; or other conditions that may lead to reduced lactase expression in the small intestine.

Clinical Diagnosis

Mucosal biopsy of the duodenum followed by biochemical lactase assay to directly measure lactase activity is the criterion standard for diagnosing lactase insufficiency. Although this approach also

may exclude other causes of secondary lactose malabsorption, the utilityis limited due to the invasiveness of the procedure and the patchy expression of lactase in the duodenum.

Two common alternatives to this direct method of measuring lactase activity are the HBT and the lactose tolerance blood test, which measure lactose malabsorption. Because lactose malabsorption is nearly always attributable to lactase insufficiency, insufficiency typically can be imputed from the assessment of lactose malabsorption.

The HBT measures by gas chromatography the amount of hydrogen exhaled for up to 3 hours after ingesting 25 to 50 g of lactose. Persons undergoing HBT are required to fast overnight and refrain from activities that may elevate breath hydrogen during testing. A rise in breath hydrogen of 0.31 to 2.5 mL/min is indicative of bacterial fermentation from malabsorbed lactose. A negative HBT can exclude lactose malabsorption as the cause of symptoms, and a positive result indicates that symptoms may be attributable to lactose ingestion. The following factors are associated with increased breath hydrogen and may cause false-positive results if present at the time of testing:

- Diabetes
- Small bowel disease (eg, celiac, giardiasis)
- Bacterial overgrowth
- Altered colon pH
- Antibiotic usage
- Probiotic usage
- Smoking
- Exercise
- Aspirin usage
- Colonic bacterial adaptation.

The lactose tolerance blood test measures blood glucose increase over time with blood drawn at 15, 30, 60, and 90 minutes after ingesting a 25- to 50-g dose of lactose. A glucose increase of less than 20 mg/dL above an 8-hour fasting level indicates an abnormal test. The following factors are associated with increased blood sugar when undergoing a lactose tolerance test and may cause false-positive results:

- Diabetes
- Small bowel disease (eg, celiac, giardiasis)
- Thyroid disorders

- Motility disorders (stomach, small bowel)
- Bacterial overgrowth.

Molecular Diagnosis
Enattah et al (2002) identified the first DNA variant to control transcription of lactase. This variant (*MCM6* -13910C>T) is located in a noncoding region of the *MCM6* gene that is upstream of the lactase gene (*LCT*). The less common T allele has been associated with lactase persistence and has demonstrated an autosomal dominant pattern of inheritance. This variant is thought to be related to the domestication of animals during the last 10,000 to 12,000 years, and persons with the C/C genotype have been shown to be associated strongly with a lactase insufficiency phenotype in whites. Other variants in the same *MCM6* regulatory region are associated with other ethnic groups (eg, Africans, Arabs), but prevalence varies geographically and, to date, no commercially available testing kits have incorporated these variants.

Prometheus's *Lacto*TYPE®‡ is a commercially available polymerase chain reaction-based test that assesses the most common lactase non persistence variant (*MCM6* -13910C>T) in patients with suspected lactose intolerance. Fulgent Clinical Diagnostics Lab also offers *MCM6* sequencing as well as deletion and duplication analysis using next-generation sequencing. Demonstration of the C/C genotype can be used as indirect evidence of lactase insufficiency and lactose malabsorption.

Treatment
The goal of treatment should be to ensure adequate nutrition for skeletal health. For patients with lactase insufficiency, dietary adjustment to restrict the consumption of foods containing lactose is the principal form of therapy. However, even lactose mal digesters can usually tolerate small amounts of lactose (12 g/d) with no or minimal symptoms. Lactase enzyme preparations are available for symptom relief but may not be effective in all patients.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be

licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Rationale/Source

Genetic testing of adults with suspected lactase insufficiency is proposed as an alternative to current diagnostic practices, which include hydrogen breath test, lactose tolerance blood test, and intestinal biopsy.

For individuals with suspected lactase insufficiency who receive targeted testing for the MCM6 -13910C>T variant, the evidence includes genotype-phenotype studies and a meta-analysis. Relevant outcomes are symptoms, morbid events, functional outcomes, health status measures, and quality of life. Studies have demonstrated a high correlation between the -13910C>T single nucleotide variant upstream of the gene encoding the enzyme lactase, and lactase insufficiency in persons of European ancestry. Studies in white populations have reported a high degree of agreement for the diagnosis of lactase insufficiency between genotyping and both hydrogen breath test and lactose tolerance blood test. However, there is no current treatment for lactase insufficiency, and management involves dietary restriction and palliation of lactose intolerance symptoms. Therefore, an empirical diagnosis of lactose intolerance in the absence of confirmation by hydrogen breath test, lactose tolerance blood test, or genotyping, followed by treatment with dietary restriction of lactose, is suitable. Currently, the evidence does not support the conclusion that assessment of the genetic etiology of lactose intolerance would affect patient management or improve clinical outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Practice Guidelines and Position Statements
No guidelines or statements were identified.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in April 2018 did not identify any ongoing or unpublished trials that would likely influence this review.

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Policy History

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06/27/2013	Medical Policy Committee review
07/17/2013	Medical Policy Implementation Committee approval. New policy.
07/10/2014	Medical Policy Committee review
07/16/2014	Medical Policy Implementation Committee approval. No change to coverage.
06/25/2015	Medical Policy Committee review
07/15/2015	Medical Policy Implementation Committee approval. No change to coverage.
06/30/2016	Medical Policy Committee review
07/20/2016	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
07/06/2017	Medical Policy Committee review
07/19/2017	Medical Policy Implementation Committee approval. No change to coverage.
07/05/2018	Medical Policy Committee review
07/11/2018	Medical Policy Implementation Committee approval. Coverage statement reworded.
07/03/2019	Medical Policy Committee review
07/18/2019	Medical Policy Implementation Committee approval. No change to coverage.
07/02/2020	Medical Policy Committee review
07/08/2020	Medical Policy Implementation Committee approval. No change to coverage.

Next Scheduled Review Date: 07/2021

Coding

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	81400
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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