2.04.94	Genetic Testing for Lactase Insufficiency		
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Section:	2.0 Medicine	**Page:**	Page 1 of 14

Policy Statement

I. The use of targeted *MCM6* -13910C>T variant analysis for the prediction of lactase insufficiency is considered **investigational**.

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

Policy Guidelines

Genetics Nomenclature Update

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

The American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) 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 individuals 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 individuals ; 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.

Coding
The following test is included under CPT code 81400 (Molecular pathology procedure, Level 1):
LCT (lactase-phlorizin hydrolase) (e.g., lactose intolerance), 13910 C>T variant.

Description

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.

Related Policies

- N/A

Benefit Application

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

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

Regulatory Status

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 (CLIA). Laboratories that offer laboratory-developed tests must be licensed by the CLIA 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

Background
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.[1,]

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.[2,]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).[3,] Ethnic groups with the highest prevalences of lactase insufficiency are Asian, Native American, and Black, 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).[4]
[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 nonpersistence 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.[5] 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.[6] 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.[5]

Lactose Intolerance
Lactose intolerance indicates that lactose malabsorption causes gastrointestinal symptoms. There is no genetic test for lactose intolerance; demonstration of lactose intolerance requires individuals to self-report symptoms (see Table 2) 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.[3] Jellema et al (2010) indicated in their meta-analysis that no specific complaint could predict lactose malabsorption; for common lactose intolerance symptoms, sensitivity and specificity ranged from 0% to 90% and 18% to 96%, respectively.[7] Similarly, 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 Individuals Who Experience Symptoms, %
Gut-related symptoms	
Abdominal pain	100
Gut distension	100
Borborygmi (stomach rumbling)	100
Flatulence	100
Diarrhea	70
Nausea	78
Vomiting	78

Symptoms	Percent of Total Individuals Who Experience Symptoms, %
Constipation	30
Systemic symptoms	
Headache and lightheadedness	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).[2,]

Symptoms

Lactase insufficiency is common, occurring in approximately 70% of persons after weaning.[8,] 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.[9,] 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.[6,]

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 utility is 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.[3,]

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.[3,] 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 (e.g., 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 (e.g., 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.[10,] 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 (e.g., Africans, Arabs), but prevalence varies geographically[6,11,] 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 nonpersistence variant (*MCM6* -13910C>T) in individuals 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.[1,] For individuals with lactase insufficiency, dietary adjustment to restrict the consumption of foods containing lactose is the principal form of therapy. However, even lactose maldigesters 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 individuals.

Literature Review

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other

Suspected Lactase Insufficiency

Clinical Context and Test Purpose

The purpose of targeted testing for the *MCM6* -13910C>T variant in adults who have suspected lactase insufficiency is to inform a decision whether to undergo the hydrogen breath test (HBT), lactose tolerance blood test (LTT), or biopsy.

The question addressed in this evidence review is: Does testing for the *MCM6* -13910C>T variant in adults who have suspected lactase insufficiency improve their net health outcome?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with suspected lactase insufficiency.

Interventions

The test being considered is targeted testing for the *MCM6* -13910C>T variant.

Comparators

The following practice is currently being used: empirical diagnosis by dietary restrictions.

Outcomes

The potential beneficial outcomes of primary interest include establishing a molecular genetic diagnosis of lactase insufficiency to inform management decisions based on test results.

The time frame for outcome measures varies from several weeks to months for the improvement of symptoms to long-term alleviation of symptoms.

Study Selection Criteria

Below are selection criteria for studies to assess whether a test is clinically valid.

- The study population represents the population of interest. Eligibility and selection are described.
- The test is compared with a credible reference standard.
- If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
- Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (e.g., ROC, AUROC, c-statistic, likelihood ratios) may be included but are less informative.
- Studies should also report reclassification of diagnostic or risk category.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Many studies have evaluated the diagnosis of lactase insufficiency using polymerase chain reaction variant analysis of *MCM6* -13910C>T, and those that have assessed the agreement between genotyping and HBT, LTT, or biopsy are presented in Table 3. Nineteen studies have compared genotyping of the single nucleotide variant (SNV) -13910C>T with HBT and found sensitivities and specificities ranging from 71% to 100% and 64% to 100%, respectively. Five studies compared genotyping with LTT and reported sensitivities and specificities ranging from 85% to 100% and 87% to 95%, respectively. Enko et al (2014) compared genotyping with a hydrogen/ methane breath test, which may be more sensitive than HBT, and reported moderate agreement (Cohen's k=0.44).[12,] Heterogeneity in study populations, a dose of lactose given during the HBT and LTT, and age of participants contributed to the wide range of observed sensitivities and specificities. Direct comparison of these tests is not possible because no identified studies compared both genotyping and HBT or LTT with the criterion standard of

duodenal mucosal biopsy. The indirect comparison is also not possible because of the small number of studies comparing genotyping, HBT, or LTT with biopsy.

The incomplete agreement is expected between genotyping for lactase insufficiency and indirect tests of lactose malabsorption because these tests do not measure the same parameters. LTT and HBT are intended to diagnose lactose malabsorption, which can be caused by factors other than lactase insufficiency. Additionally, because lactase activity persists for years after weaning, the inclusion of children can affect the concordance between HBT or LTT and genotyping. Di Stefano et al (2009) found that the overall k value for agreement between HBT and genotyping was 0.74, but for those younger than and older than 30 years of age, k values were 0.56 and 1.0, respectively (p<0.005 for both comparisons).[13]

The SNV -13910C>T is not the only *MCM6* variant implicated in regulating transcription of the lactase (*LCT*) gene. Eadala et al (2011) recruited patients with inflammatory bowel disease along with healthy control patients and found that, although the C/C genotype was strongly associated with experiencing symptoms of lactose intolerance after HBT, there was a high proportion of lactose sensitivity in C/T and T/T genotype patients as well.[14] Mendoza Torres et al (2012) found low specificity (46%) when comparing HBT with genotyping.[15] The authors attributed this to the genetic heterogeneity of the Colombian and Caribbean population studied, and recommended against using genotyping to assess lactase insufficiency in this population. Santonocito et al (2015) found a similar proportion (≈80%) of homozygous genotypes for lactase nonpersistence among 1426 patients with gastrointestinal symptoms and 1000 healthy volunteers in south-central Italy.[16] These results would suggest that unmeasured genetic variation may more fully explain lactase insufficiency.

Table 3. Reported Sensitivities and Specificities Between Genotyping and HBT, LTT, and Intestinal Biopsy[a]

Study, Country	N	Sensitivity (95% CI), %	Specificity (95% *CI*), %
Targeted variant analysis of SNV -13910C>T vs. HBT			
Gugatschka et al (2005), Austria[17]	51	90 (73 to 98)	95 (76 to 100)
Buning et al (2005), Germany[18]	166	98 (93 to 100)	83 (71 to 91)
Hogenauer et al (2005), Austria[9]	123	97 (86 to 100)	86 (77 to 93)
Bulhoes et al (2007), Brazil[19]	20	90 (55 to 100)	100 (69 to 100)
Schirru et al (2007), Italy[20]	84	84 (72 to 93)	96 (81 to 100)
Bernardes-Silva et al (2007), Brazil[21]	147	76 (59 to 89)	100 (40 to 100)
Szilagyi et al (2007), Canada[22]	30	93 (68 to 100)	80 (52 to 96)
Kerber et al (2007), Austria[23]	120	97 (86 to 100)	72 (61 to 95)
Mattar et al (2008), Brazil[24]	50	96 (82 to 100)	100 (85 to 100)
Krawczyk et al (2008), Germany[25]	58	100 (78 to 100)	95 (84 to 99)
Mottes et al (2008), Italy[26]	112	71 (60 to 80)	83 (61 to 95)
Waud et al (2008), Wales[27]	200	100 (88 to 100)	64 (57 to 71)
Di Stefano et al (2009), Italy[13]	32	88 (70 to 98)	100 (54 to 100)
Nagy et al (2009), Hungary[28]	186	77 (68 to 85)	94 (87 to 98)
Szilagyi et al (2009), Canada[29]	57	97 (83 to 100)	93 (76 to 99)
Babu et al (2010), India[30]	153	87 (80 to 93)	97 (85 to 100)
Pohl et al (2010), Germany[31]	194	90 (80 to 96)	98 (94 to 100)
Mendoza Torres et al (2012), Columbia[15]	126	97	46
Morales et al (2011), Chile[32]	51	96.3	87.5
Targeted variant analysis of SNV -13910C>T vs. H/MBT			
Enko et al (2014), Austria[12]	263	79	87
Targeted variant analysis of SNV -13910C>T vs. LTT			
Nilsson et al (2004), Sweden[33]	35	100	88
Gugatschka et al (2005), Austria[17]	46	85	90
Ridefelt et al (2005), Canada[34]	51	90	95
Szilagyi et al (2007), Canada[22]	30	93	87
Babu et al (2010), India[30]	153	97	87
Targeted variant analysis of -13910C>T vs. biopsy-determined lactase activity			
Rasinpera et al (2004), Finland[35]	329 <5 y: 109	NA 80	NA 65.4

Study, Country	N	Sensitivity (95% CI), %	Specificity (95% *CI), %*
	6-11 y:	94.6	81.9
	142	93.3	100
	≥12 y: 78		
Nilsson et al (2004), Sweden[33,]	35	100	88
	176[b]	NA	NA
Kuchay et al (2011), India[36,]	>5 y: 108[b]	96	78.9
	>8 y: NR	97.2	100
Mattar et al (2013), Brazil[37,]	32	100	48
Targeted variant analysis of -22018G>A vs. HBT			
Bernardes-Silva et al (2007), Brazil[21,]	147	73	82
Kerber et al (2007), Austria[23,]	166	100	71
Di Stefano et al (2009), Italy[13,]	123	89	100

CI; confidence interval; HBT: hydrogen breath test; H/MBT: hydrogen methane breath test; LTT: lactose tolerance blood test; NA: not applicable; NR: not reported; SNV: single nucleotide variant.
[a] There was heterogeneity in how the HBT and LTT were conducted (e.g., using 25 g or 50 g of lactose) and in populations tested (e.g., inclusion of children or racial/ethnic composition of study populations).
[b] Children.

Marton et al (2012) compared the diagnostic accuracy of HBT and LTT testing with -13910C>T genotyping for prediction of lactase insufficiency phenotype.[38,] Seventeen studies evaluated HBT, and 5 evaluated LTT. Overall sensitivity and specificity of HBT were 88% (95% confidence interval [CI], 85% to 90%) and 85% (95% CI, 82% to 87%), respectively. Both sensitivity and specificity showed substantial heterogeneity (I^2=78% and 87%, respectively), and reviewers detected potential publication bias. For LTT, overall sensitivity was 94% (95% CI, 90% to 97%) and specificity was 90% (95% CI, 84% to 95%). No significant statistical heterogeneity was observed. Three studies also assessed -22018G>A genotype, which has been described in European populations, and found less accurate overall sensitivity (87%; 95% CI, 79% to 93%) and specificity (76%; 95% CI, 67% to 83%), compared with the -13910C>T variant.

Section Summary: Clinically Valid
Evidence of clinical validity for variant analysis of -13910C>T includes genotype-phenotype correlation studies and a meta-analysis. Discordance between genotyping for lactase insufficiency and indirect tests of lactose malabsorption such as LTT and HBT have been noted given that lactose malabsorption can be caused by factors other than lactase insufficiency. Studies have demonstrated that analysis of the -13910C>T variant can detect lactase insufficiency.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

No studies were identified that attempted to demonstrate improved patient outcomes or changes in patient management because of genetic testing for lactase insufficiency.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Lactase insufficiency is the normal phenotype for most adults, and a confirmatory diagnosis with HBT, LTT, or genotyping is unnecessary. Empirical diagnosis by dietary restriction is adequate in

most circumstances because this is the primary treatment for lactase insufficient patients. Patients who achieve satisfactory symptom control after dietary modification require no further diagnostic testing. For most patients who do not achieve symptom control after dietary modification, testing is indicated for the presence of other conditions that can cause similar symptoms.

The proposed clinical utility of genotyping for lactase insufficiency is that the test offers a more comfortable assessment for patients when compared with HBT, LTT, or biopsy. Traditional testing methods may be associated with discomfort caused by the ingestion of a large volume of lactose, and there are dietary preparations and fasting before testing. Additionally, factors that may cause false-positive HBT, and LTT results will not cause false-positive genotype results. Arroyo et al (2010) suggested that genetic testing, when used with HBT, can help in the diagnosis of secondary hypolactasia when there is a positive HBT and the patient is not -13910C/C genotype.[39,]

Section Summary: Clinically Useful
Direct evidence for the clinical utility of genotyping for lactase insufficiency is lacking. Genetic testing has the potential advantage of sparing patients the discomfort of fasting and experiencing symptoms of lactose intolerance during the administration of HBT, LTT, or biopsy. However, meaningful improvements in health outcomes through the use of genotyping for lactase insufficiency have not been demonstrated.

Summary of Evidence
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 that the technology results in an improvement in the net health outcome.

Supplemental Information
The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

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.

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in April 2022 did not identify any ongoing or unpublished trials that would likely influence this review.

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Documentation for Clinical Review

- No records required

Coding

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

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

Type	Code	Description
CPT®	81400	Molecular pathology procedure level 1
HCPCS	None	

Policy History

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

Effective Date	Action
08/31/2015	BCBSA Medical Policy adoption
03/01/2017	Policy revision without position change
11/01/2017	Policy revision without position change
07/01/2018	Policy revision without position change
07/01/2019	Policy revision without position change
07/01/2020	Annual review. No change to policy statement. Literature review updated.
07/01/2021	Annual review. No change to policy statement. Literature review updated.
07/01/2022	Annual review. No change to policy statement. Literature review updated.

Definitions of Decision Determinations

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

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

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

Prior Authorization Requirements (as applicable to your plan)

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

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

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

Appendix A

POLICY STATEMENT	
BEFORE	**AFTER** **Blue font: Verbiage Changes/Additions**
Genetic Testing for Lactase Insufficiency 2.04.94 **Policy Statement:** The use of targeted *MCM6* -13910C>T variant analysis for the prediction of lactase insufficiency is considered **investigational**.	**Genetic Testing for Lactase Insufficiency 2.04.94** **Policy Statement:** I. The use of targeted *MCM6* -13910C>T variant analysis for the prediction of lactase insufficiency is considered **investigational**.