BlueCross BlueShield of Alabama

Name of Policy:
Genetic Testing for Lactase Insufficiency

Policy #: 588
Category: Laboratory

Latest Review Date: May 2018
Policy Grade: D

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *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 that patient's illness, injury or disease.*

Description of Procedure or Service:

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

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 for rare instances of congenital hypolactasia, most infants are able to 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.

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, two 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 (lactasepersistence). Ethnic groups with the highest prevalences of lactase insufficiency are Asian, Native American, and blacks, with the lowest prevalences in people of northern European origin (Table 1).

Table 1. Prevalence of Lactase Insufficiency by Ethnicity

Population	Percent Lactase Insufficiency[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

[a]Identified through hydrogen breath test (HBT) or lactose tolerance blood test (LTT).

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. 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 ten 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 (LLT).

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 (listed in 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. A 2010 meta-analysis by Jellema et al 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	% of Total Patients Who Experience Symptom
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

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, the 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; 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. In addition, 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 which 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, 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 LTT, which measure lactose malabsorption. Because lactose malabsorption is nearly always attributable to lactase insufficiency, insufficiency typically can be imputed from assessment of lactose malabsorption.

The HBT measures by gas chromatography the amount of hydrogen exhaled for up to three 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 (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 eight-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

In 2002, Enattah et al identified the first DNA variant to control transcription of lactase. This variant, (*MCM6* –13910 C>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 strongly associated with a lactase insufficiency phenotype in whites. Other variants in the same *MCM6* regulatory region are associated with other ethnic groups (such as Africans and Arabs), but the prevalences of these vary geographically and to date, no commercially available testing kits have incorporated these variants.

Prometheus's (San Diego, CA) LactoType® is a commercially available polymerase chain reaction (PCR)-based test that assesses the most common lactase nonpersistence variant, *MCM6* – 13910 C>T, in patients with suspected lactose intolerance. Fulgent Clinical Diagnostics Lab (Temple City, CA) also offers *MCM6* sequencing and deletion/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 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 patients.

Policy:

The use of targeted variant analysis of *MCM6* – 13910 C>T for the prediction of lactase insufficiency does not meet Blue Cross Blue Shield of Alabama's medical criteria for coverage and is considered i**nvestigational**.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

The most recent literature review was performed through March 6, 2018.

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 sources.

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 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 the net health outcome?

The following PICOTS were used to select literature to inform this review.

Patients

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

Interventions

The relevant intervention of interest is targeted testing for the *MCM6* -13910C>T variant.

Comparators

The relevant comparator of interest are dietary restrictions.

Outcomes

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

Timing

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

Setting

Patients with suspected lactase insufficiency are managed in primary care and may be referred to gastroenterology.

There are three core characteristics for assessing a medical test. Whether imaging, laboratory, or other, all medical tests must be:

- Technically reliable
- Clinically valid
- Clinically useful.

Because different specialties may use different terms for the same concept, we are highlighting the core characteristics. The core characteristics also apply to different uses of tests, such as diagnosis, prognosis, and monitoring treatment.

Diagnostic tests detect presence or absence of a condition. Surveillance and treatment monitoring are essentially diagnostic tests over a time frame. Surveillance to see whether a condition develops or progresses is a type of detection. Treatment monitoring is also a type of detection because the purpose is to see if treatment is associated with the disappearance, regression, or progression of the condition.

Prognostic tests predict the risk of developing a condition in the future. Tests to predict response to therapy are also prognostic. Response to therapy is a type of condition and can be either a beneficial response or adverse response. The term predictive test is often used to refer to the response to therapy. To simplify terms, we use prognostic to refer both to predicting a future condition or predicting response to therapy.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

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).

Many reports on the diagnosis of lactase insufficiency by polymerase chain reaction (PCR) variant analysis of *MCM6*–13910 C>T have been published, and those that assess the agreement between genotyping and hydrogen breath test (HBT), lactose tolerance blood test (LTT) or biopsy are presented in Table 3. Nineteen studies compared genotyping of single nucleotide variant (SNV) –13910 C>T to HBT and found sensitivities and specificities ranging from 71% to 100% and 64% to 100%, respectively. Five studies compared genotyping with LTT with sensitivities and specificities ranging from 85% to 100% and 87% to 95%, respectively. The study by Enko et al (2014) compared genotyping to a hydrogen/methane breath test, which may be more sensitive than HBT, and reported Cohen's kappa statistic of 0.44, indicating moderate agreement. Heterogeneity in study populations, dose of lactose given in HBT/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/LTT with the criterion standard of duodenal mucosal biopsy. Indirect comparison is

not possible because of the small number of studies comparing genotyping, HBT, or LTT to biopsy.

The incomplete agreement is expected between genotyping for lactase insufficiency and indirect tests of lactose malabsorption is expected because these tests do not measure the same parameters. LTT and HBT are intended to diagnosis 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/LTT and genotyping. Di Stefano et al (2009) found that the overall kappa value for agreement of HBT and genotyping was 0.74, but for those younger than and older than 30 years of age, kappa values were 0.56 and 1.0, respectively ($p<0.005$ for both comparisons).

The SNV –13910 C>T is not the only *MCM6* variant implicated in regulating transcription of the *LCT* gene. A study by 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. A 2012 Colombian study by Mendoza- Torres et al found low specificity (46%) when comparing HBT with genotyping. The authors attributed this to the genetic heterogeneity of the Colombian and Caribbean population studied and recommend against using genotyping to assess lactase insufficiency in this population. Similarly, Santonocito et al in 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. These results suggest that unmeasured genetic variation may more fully explain lactase insufficiency.

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

Author, Year, County	N	Sensitivity (95% CI)	Specificity (95% CI)
Targeted variant analysis of SNV -13910 C>T vs HBT			
Gugatschka (2005), Austria	51	90 (73 to 98)	95 (76 to 100)
Buning (2005), Germany	166	98 (93 to 100)	83 (71 to 91)
Hogenauer (2005), Austria	123	97 (86 to 100)	86 (77 to 93)
Bulhoes (2007), Brazil	20	90 (55 to 100)	100 (69 to 100)
Schirru (2007), Italy	84	84 (72 to 93)	96 (81 to 100)
Bernardes (2007), Brazil	147	76 (59 to 89)	100 (40 to 100)
Szilagyi (2007), Canada	30	93 (68 to 100)	80 (52 to 96)
Kerber (2007), Austria	120	97 (86 to 100)	72 (61 to 95)
Mattar (2008), Brazil	50	96 (82 to 100)	100 (85 to 100)
Krawcyk (2008), Germany	58	100 (78 to 100)	95 (84 to 99)
Mottes (2008), Italy	112	71 (60 to 80)	83 (61 to 95)
Waud (2008), Wales	200	100 (88 to 100)	64 (57 to 71)
Di Stefano (2009), Italy	32	88 (70 to 98)	100 (54 to 100)
Nagy (2009), Hungary	186	77 (68 to 85)	94 (87 to 98)
Szilagyi (2009), Canada	57	97 (83 to 100)	93 (76 to 99)
Babu (2010), India	153	87 (80 to 93)	97 (85 to 100)
Pohl (20100, Germany	194	90 (80 to 96)	98 (94 to 100)
Mendoza-Torres (2012), Columbia	126	97	46
Morales (2011), Chile	51	96.3	87.5

Targeted variant analysis of SNV -13910C>T vs H/MBT			
Enko et al (2015), Austria	263	79	87
Targeted variant analysis of -22018 G>A with HBT			
Bernardes (2007), Brazil	147	73	82
Kerber (2007), Austria	166	100	71
Di Stefano (2009), Italy	123	89	100
Targeted variant analysis of SNV –13910 C>T vs LTT			
Nilsson (2004), Sweden	35	100	88
Gugatschka (2005), Austria	46	85	90
Ridefelt (2005), Canada	51	90	95
Szilagyi (2007), Canada	30	93	87
Babu (2010), India	153	97	87
Targeted variant analysis of –13910 C>T vs biopsy determined lactase level			
Rasinpera (2004), Finland	329 <5 y: 109 6-11 y: 142 ≥12 y: 78	– 80 94.6 93.3	– 65.4 81.9 100
Nilsson (2004), Sweden	35	100	88
Kuchay (2011), India	176 Children >5: 108 Children >8: NR	– 96 97.2	– 78.9 100
Mattar (2013), Brazil	32	100	48

CI; confidence interval; HBT: hydrogen breath test; H/MBT: hydrogen methane breath test; LTT: lactose tolerance blood test; NR: not reported; SNV: single-nucleotide variant

populations tested (e.g., inclusion of children or racial/ethnic composition of study populations).

A 2012 meta-analysis by Marton et al compared the diagnostic accuracy of HBT/LTT testing with -13910C>T genotyping for prediction of lactase insufficiency phenotype. Seventeen studies evaluated HBT, and five evaluated LTT. Overall sensitivity and specificity of HBT was 88% (95% confidence interval [CI], 85% to 90%) and 85% (95% CI, 82% to 87%), respectively. Both sensitivity and specificity showed substantial heterogeneity (I2=78% and 87%, respectively), and the authors 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 the -22018G>A genotype, which has been described in European populations, and found less accurate overall sensitivity and specificity (87% [95% CI, 79% to 93%] and 76% [95% CI, 67% to 83%], respectively) compared with the -13910C>T variant.

Section Summary: Clinically Valid

Evidence of clinical validity for variant analysis of -13910C>T include genotype-phenotype correlation studies and 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 by caused by factors other than lactase insufficiency. Studies have demonstrated that variant analysis of -13910C>T is able to 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 generally unnecessary. Empiric 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 is dietary preparation 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 –13910 C/C genotype.

Section Summary: Clinical Utility
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 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 HBT and LTT. 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 HBT, LTT, or genotyping, followed by treatment with dietary restriction of lactose, is suitable. Currently the evidence does not support 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.

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

U.S. Preventive Services Task Force
Not applicable.

Key Words:

Lactase insufficiency, lactose malabsorption , LTT, *MCM6*, Prometheus's LactoType®, *LCT* gene, –13910 C>T

Approved by Governing Bodies:

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.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply.
FEP: Special benefit consideration may apply. Refer to member's benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Current Coding:

CPT Codes:

81400	Molecular pathology procedure, level 1 (e.g., identification of single germline variant [e.g., SNV] by techniques such as restriction enzyme digestion or melt curve analysis) includes the following test effective 7/1/2013): *LCT (lactase-phlorizin hydrolase)* (e.g., lactose intolerance), -13910 C>T variant

References:

1. Arroyo MA, Lopes A, Piatto V et al. Perspectives for Early Genetic Screening of Lactose Intolerance: - 13910C/T Polymorphism Tracking in the MCM6 Gene. Open Biol J 2010; 3:66-71.
2. Babu J, Kumar S, Babu P et al. Frequency of lactose malabsorption among healthy southern and northern Indian populations by genetic analysis and lactose hydrogen breath and tolerance tests. Am J Clin Nutr 2010; 91(1):140-6.
3. Bernardes-Silva CF, Pereira AC, de Fatima Alves da Mota G et al. Lactase persistence/nonpersistence variants, C/T_13910 and G/A_22018, as a diagnostic tool for lactose intolerance in IBS patients. Clin Chim Acta 2007; 386(1-2):7-11.
4. Bulhoes AC, Goldani HA, Oliveira FS et al. Correlation between lactose absorption and the C/T- 13910 and G/A-22018 mutations of the lactase-phlorizin hydrolase (LCT) gene in adult-type hypolactasia. Braz J Med Biol Res 2007; 40(11):1441-6.
5. Buning C, Genschel J, Jurga J et al. Introducing genetic testing for adult-type hypolactasia. Digestion 2005; 71(4):245-50.
6. Di Stefano M, Terulla V, Tana P et al. Genetic test for lactase non-persistence and hydrogen breath test: is genotype better than phenotype to diagnose lactose malabsorption? Dig Liver Dis 2009; 41(7):474-9.
7. Eadala P, Matthews SB, Waud JP et al. Association of lactose sensitivity with inflammatory bowel disease--demonstrated by analysis of genetic polymorphism, breath gases and symptoms. Aliment Pharmacol Ther 2011; 34(7):735-46.
8. Enattah NS, Sahi T, Savilahti E et al. Identification of a variant associated with adult-type hypolactasia. Nat Genet 2002; 30(2):233-7.
9. Enko D, Rezanka E, Stolba R, Halwachs-Baumann G. Lactose malabsorption testing in daily clinical practice: a critical retrospective analysis and comparison of the hydrogen/methane breath test and genetic test (c/t-13910 polymorphism) results. Gastroenterol Res Pract. 2014;2014:464382.
10. Gugatschka M, Dobnig H, Fahrleitner-Pammer A et al. Molecularly-defined lactose malabsorption, milk consumption and anthropometric differences in adult males. QJM 2005; 98(12):857-63.
11. Haberkorn BC, Ermens AA, Koeken A et al. Improving diagnosis of adult-type hypolactasia in patients with abdominal complaints. Clin Chem Lab Med 2012; 50(1):119-23.
12. Hogenauer C, Hammer HF, Mellitzer K et al. Evaluation of a new DNA test compared with the lactose hydrogen breath test for the diagnosis of lactase non-persistence. Eur J Gastroenterol Hepatol 2005; 17(3):371-6.
13. Jellema P, Schellevis FG, van der Windt DA et al. Lactose malabsorption and intolerance: a systematic review on the diagnostic value of gastrointestinal symptoms and self-reported milk intolerance. QJM 2010; 103(8):555-72.
14. Kerber M, Oberkanins C, Kriegshauser G et al. Hydrogen breath testing versus LCT genotyping for the diagnosis of lactose intolerance: a matter of age? Clin Chim Acta 2007; 383(1-2):91-6.

15. Krawczyk M, Wolska M, Schwartz S et al. Concordance of genetic and breath tests for lactose intolerance in a tertiary referral centre. J Gastrointestin Liver Dis 2008; 17(2):135-9.
16. Kuchay RA, Thapa BR, Mahmood A et al. Effect of C/T -13910 cis-acting regulatory variant on expression and activity of lactase in Indian children and its implication for early genetic screening of adult-type hypolactasia. Clin Chim Acta 2011; 412(21-22):1924-30.
17. Marton A, Xue X, Szilagyi A. Meta-analysis: the diagnostic accuracy of lactose breath hydrogen or lactose tolerance tests for predicting the North European lactase polymorphism C/T-13910. Aliment Pharmacol Ther 2012; 35(4):429-40.
18. Mattar R, Basile-Filho A, Kemp R et al. Comparison of Quick Lactose Intolerance Test in duodenal biopsies of dyspeptic patients with single nucleotide polymorphism LCT-13910C>T associated with primary hypolactasia/lactase-persistence. Acta Cir Bras 2013; 28 Suppl 1:77-82.
19. Mattar R, Monteiro Mdo S, Villares CA et al. Single nucleotide polymorphism C/T(-13910), located upstream of the lactase gene, associated with adult-type hypolactasia: validation for clinical practice. Clin Biochem 2008; 41(7-8):628-30.
20. Matthews SB, Waud JP, Roberts AG et al. Systemic lactose intolerance: a new perspective on an old problem. Postgrad Med J 2005; 81(953):167-73.
21. Mendoza Torres E, Varela Prieto LL, Villarreal Camacho JL et al. Diagnosis of adult-type hypolactasia/lactase persistence: genotyping of single nucleotide polymorphism (SNP C/T-13910) is not consistent with breath test in Colombian Caribbean population. Arq Gastroenterol 2012; 49(1):5-8.
22. Misselwitz B, Pohl D, Frühauf H et al. Lactose malabsorption and intolerance: pathogenesis, diagnosis and treatment. United European Gastroenterol J 2013.
23. Morales E, Azocar L, Maul X et al. The European lactase persistence genotype determines the lactase persistence state and correlates with gastrointestinal symptoms in the Hispanic and Amerindian Chilean population: a case-control and population-based study. BMJ Open 2011; 1(1):e000125.
24. Mottes M, Belpinati F, Milani M et al. Genetic testing for adult-type hypolactasia in Italian families. Clin Chem Lab Med 2008; 46(7):980-4.
25. Nagy D, Bogacsi-Szabo E, Varkonyi A et al. Prevalence of adult-type hypolactasia as diagnosed with genetic and lactose hydrogen breath tests in Hungarians. Eur J Clin Nutr 2009; 63(7):909-12.
26. National Center for Biotechnology Information. Genetic Testing Registry (GTR). MCM6: performance characteristics, last updated: 2014-09-24. www.ncbi.nlm.nih.gov/gtr/tests/518150/performance-characteristics/. Accessed March 11, 2015.
27. National Institutes of Health. Lactose Intolerance and Health. Paper presented at: NIH Consensus Development Conference:2010.
28. Nilsson TK, Johansson CA. A novel method for diagnosis of adult hypolactasia by genotyping of the - 13910 C/T polymorphism with Pyrosequencing technology. Scand J Gastroenterol 2004; 39(3):287-90.
29. Pohl D, Savarino E, Hersberger M et al. Excellent agreement between genetic and hydrogen breath tests for lactase deficiency and the role of extended symptom assessment. Br J Nutr 2010; 104(6):900-7.

30. Rasinpera H, Savilahti E, Enattah NS et al. A genetic test which can be used to diagnose adult-type hypolactasia in children. Gut 2004; 53(11):1571-6.
31. Raz M, Sharon Y, Yerushalmi B et al. Frequency of LCT-13910C/T and LCT-22018G/A single nucleotide polymorphisms associated with adult-type hypolactasia/lactase persistence among Israelis of different ethnic groups. Gene 2013; 519(1):67-70.
32. Ridefelt P, Hakansson LD. Lactose intolerance: lactose tolerance test versus genotyping. Scand J Gastroenterol 2005; 40(7):822-6.
33. Sahi T. Genetics and epidemiology of adult-type hypolactasia. Scand J Gastroenterol Suppl 1994; 202:7-20.
34. Santonocito C, Scapaticci M, Guarino D, et al. Lactose intolerance genetic testing: is it useful as routine screening? Results on 1426 south-central Italy patients. Clin Chim Acta. Jan 15 2015;439:14-17.
35. Schirru E, Corona V, Usai-Satta P et al. Genetic testing improves the diagnosis of adult type hypolactasia in the Mediterranean population of Sardinia. Eur J Clin Nutr 2007; 61(10):1220-5.
36. Shaukat A, Levitt MD, Taylor BC et al. Systematic review: effective management strategies for lactose intolerance. Ann Intern Med 2010; 152(12):797-803.
37. Suchy FJ, Brannon PM, Carpenter TO, et al. National Institutes of Health Consensus Development Conference: lactose intolerance and health. Ann Intern Med. Jun 15 2010; 152(12):792-796.
38. Szilagyi A, Malolepszy P, Hamard E et al. Comparison of a real-time polymerase chain reaction assay for lactase genetic polymorphism with standard indirect tests for lactose maldigestion. Clin Gastroenterol Hepatol 2007; 5(2):192-6.
39. Szilagyi A, Shrier I, Chong G et al. Lack of effect of lactose digestion status on baseline fecal micoflora. Can J Gastroenterol 2009; 23(11):753-9.
40. Waud JP, Matthews SB, Campbell AK. Measurement of breath hydrogen and methane, together with lactase genotype, defines the current best practice for investigation of lactose sensitivity. Ann Clin Biochem 2008; 45(Pt 1):50-8.
41. Wilt TJ, Shaukat A, Shamliyan T et al. Lactose intolerance and health. Evid Rep Technol Assess (Full Rep) 2010; (192):1-410.

Policy History:

Medical Policy Panel, May 2013
Medical Policy Panel, May 2014
Medical Policy Group, April 2015 **(3):** Creation of individual policy with all References & Key Words related to genetic testing for lactase insufficiency removed from medical policy #136; Update to Key Points, Key Words &References; no change in policy statement.
Medical Policy Administration Committee, May 2015
Medical Policy Panel, April 2015
Medical Policy Group, May 2015 **(3)**: 2015 Updates to Description, Key Points & References; no change in policy statement
Medical Policy Panel, September 2017
Medical Policy Group, October 2017 **(3):** 2017 Updates to Description, Key Points & Approved by Governing Bodies; no references added. Changed “mutation” to “variant” in policy section but no change in policy statement intent

Medical Policy Panel, May 2018
Medical Policy Group, May 2018 **(4)**: Updates to Description, Policy, Key Points and References. Added "*MCM6*" to the policy statement. Policy statement update did not change policy intent.
