

Corporate Medical Policy

Genetic Testing for Lactase Insufficiency AHS – M2080

File Name: genetic_testing_for_lactase_insufficiency
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Description of Procedure or Service

Lactase intolerance (LI) is a common clinical syndrome defined by abdominal pain, flatulence, bloating, borborygmus and osmotic diarrhea, caused by the breakdown of nondigested lactose by the gut microflora (Ponte et al., 2016a)).

Lactose malabsorption (LM) is the nondigestion of lactose caused by low expression of the enzyme lactase and is a physiologic feature occurring in most mammals after infancy (Di Rienzo et al., 2013; Ponte et al., 2016b)

Related Policies

Diagnosis of Idiopathic Environmental Intolerance AHS – G2056

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

Genetic testing for lactase insufficiency is considered investigational for the use of targeted mutation analysis of -13910 C>T, and genetic testing of the LCT gene and/or MCM6 gene. BCBSNC does not provide coverage for investigational services or procedures.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Genetic Testing for Lactase Insufficiency is covered

N/A

When Genetic Testing for Lactase Insufficiency is not covered

The use of targeted mutation analysis of -13910 C>T for the prediction of lactase insufficiency is considered investigational.

Genetic testing of the LCT gene and/or MCM6 gene for lactose intolerance and/or lactase insufficiency is considered investigational.

Genetic Testing for Lactase Insufficiency AHS – M2080

Policy Guidelines

Background

Lactose is a disaccharide, which is a class of sugars comprised of two monosaccharides or simple sugars. Lactose consists of galactose bound to glucose and is the main source of carbohydrates from mammalian milk. Intestinal absorption of lactose requires initial hydrolysis by the enzyme lactase. Low lactase activity results in undigested lactose and colonic bacterial fermentation of that lactose. This leads to the characteristic symptoms of lactose intolerance, such as bloating and flatulence (Luyt et al., 2014).

Lactase expression decreases as consequence of the normal maturational down-regulation after weaning, ultimately to undetectable levels in most populations (Swallow, 2003). Lactase expression persists, however, in descendants of populations that traditionally practice cattle domestication who maintain the ability to digest milk and other dairy products into adulthood (Deng, Misselwitz, Dai, & Fox, 2015). Adult expression of the gene encoding lactase (LCT), located on 2q21 appears to be regulated by *cis*-acting elements (Wang et al., 1995) and is inherited as an autosomal recessive trait (Enattah et al., 2002). The LCT gene is regulated by the nearby MCM6 gene (minichromosome maintenance complex component 6), which encodes a helicase complex. To date, at least four different MCM6 variants have been identified in affecting LCT gene expression (NIH, 2019). Single nucleotide polymorphisms (SNPs) associated with the lactase persistence vary by region. In European populations it is associated with C/T-13910 and G/A-22018 (Enattah et al., 2002; Hogenauer et al., 2005; Poulter et al., 2003; Ridefelt & Hakansson, 2005), with G-13915 in Saudi Arabia (Imtiaz et al., 2007), and in African tribes with the G-14010, G-13915, and G-13907 polymorphism (Ingram et al., 2007; Tishkoff et al., 2007). No SNP associated with lactase persistence has been identified in the lactase gene regulatory sequence in Chinese populations (Zheng et al., 2016). In adult patients with homozygous lactase persistence, enzyme levels are 10-times higher than for patients with homozygous non-persistence, and heterozygous individuals (Deng et al., 2015; Enattah et al., 2007).

Lactase deficiency (LD) is defined as markedly reduced brush-border lactase activity relative to the activity observed in infants (Deng et al., 2015). Continued dairy consumption despite low expression of lactase results in unabsorbed lactose being present in the intestinal tract (lactose malabsorption [LM]), which can lead to symptoms of lactose intolerance (LI) in susceptible individuals (Hammer, 2019).

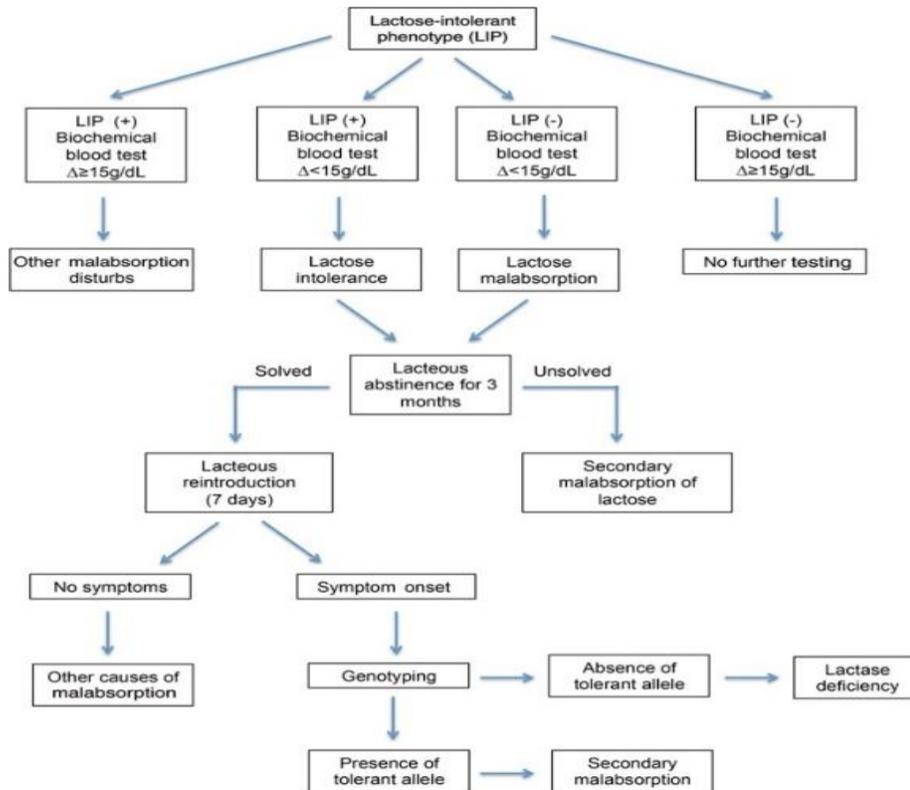
LI is defined by patient reports of abdominal pain, bloating, borborygmi, and diarrhea induced by dairy consumption. Unabsorbed lactose increases the osmotic load thus increasing the intestinal water content, resulting in osmotic diarrhea. Additionally, lactose and other poorly-absorbed oligosaccharides, disaccharides, monosaccharides, and polyols ubiquitous in the diet are readily fermented by the colonic microbiome, leading to production of short-chain fatty acids and gas (mainly hydrogen [H₂], carbon dioxide [CO₂], and methane [CH₄]) (Magge & Lembo, 2012; Shepherd, Lomer, & Gibson, 2013). LI may be associated with nonspecific symptoms, abdominal pain, bloating, flatulence, diarrhea, or vomiting (Hammer, 2018); however, it is unclear whether these symptoms are directly due to lactose ingestion. Although LM is nearly always attributable to LD, it is not possible to make a definitive diagnosis on clinical presentation alone because double-blind trials have shown that the reliability of self-reported LI is very poor (Deng et al., 2015; Suarez, Savaiano, & Levitt, 1995; Zheng et al., 2016).

Determining if reported symptoms of LI are resultant from LD can be approached through several different methods. The gold standard is the measurement of lactase, sucrose and maltase activity through intestinal biopsies. However, this method is not commonly used due to its invasive nature (Di Rienzo et al., 2013). Other tests, such as the lactose breath test or biochemical blood tests are more frequently used (Furnari et al., 2013; Mattar, Basile-Filho, Kemp, & Santos, 2013; Ponte et al., 2016b). In addition to biochemical blood tests, genetic markers may be useful for LI

Genetic Testing for Lactase Insufficiency AHS – M2080

diagnosis, however, a positive genetic test indicates whether lactase activity decline may represent a clinical problem for the patient, but the test does not give information on actual patient symptoms, making it inappropriate as an initial screening as not all patients with LM will develop symptoms of LI (Ponte et al., 2016a).

On the contrary, this information is more readily accessible by combining the lactose breath test with intolerance symptom evaluation (Di Stefano et al., 2009). Usual LI management involves excluding milk and milk products from the diet, while ensuring adequate calcium intake (Misselwitz, 2014; Ponte et al., 2016b; Usai-Satta, Scarpa, Oppia, & Cabras, 2012). The use of genetic tests has been proposed as an adjunct to LI diagnosis to differentiate primary LD from secondary causes (Bodlaj et al., 2006) as depicted below in the figure taken from Ponte et al. (2016b).



Clinical Validity and Utility

Marton, Xue, and Szilagyi (2012) compared the common polymorphism C/T 13910 with the lactase breath test and lactose tolerance test to assess each test’s ability to predict genotype/phenotype relationships. The agreement of the breath test and genotype was 0.88 sensitivity and 0.85 specificity whereas the agreement between genotype and tolerance test was 0.94 sensitivity and 0.90 specificity (Marton et al., 2012).

Baffour-Awuah et al studied the association of genotypes at the -13910 and -22018 SNPs with clinical characteristics, RNA quantification and enzymatic phenotypes among a range of European ethnicities within the U.S. population. The authors concluded that “13910T/T genotype will

Genetic Testing for Lactase Insufficiency AHS – M2080

frequently, but not perfectly, predict lactase persistence in this mixed European-ancestry population; a -13910T/C genotype will not predict the phenotype (Baffour-Awuah et al., 2015).”

Misselwitz et al. (2013) stated that genetic testing for the -13910*T genotype in certain African, Arabic, or Asian subpopulations has limited value because lactase persistence may be linked to different polymorphisms. The authors also stated that genetic tests will be negative in patients with secondary causes of lactase deficiency and that no information about clinical symptoms lactose intolerance will be obtained during testing (Misselwitz et al., 2013).

Brasen, Frischknecht, Ornskov, Andreassen, and Madsen (2017) genotyped 3395 routine samples using real-time polymerase chain reaction (PCR) for the -13910C > T-variant to determine the prevalence of the variants in a Danish cohort examined for lactose intolerance as well as to improve the real-time PCR analysis for detection of the different variants. The researchers found that “Using real-time PCR resulted in 100% successful genotyping of the -13910C > T variant. By using a quality value of 99% and sequencing the undetermined samples we improved the ability of the assay to identify variants other than -13910C > T. This resulted in a reduction of the diagnostic error rate by a factor of 2.4 while increasing the expenses only 3% (Brasen et al., 2017).”

Coluccia et al. (2019) compared results from a lactose breath test and a lactase-gene polymorphism test in a total of 158 symptomatic adults to identify lactose intolerance. Whole blood samples were used for genetic testing purposes. Lactose breath testing resulted in positive results in 75.9% of participants, while genetic testing identified lactase-gene polymorphisms in 82.3% of participants. In conclusion, the authors state, “We suggest considering the use of the genetic test after LBT [lactose breath test] administration, when secondary hypolactasia is suspected, for completion of diagnostic procedures (Coluccia et al., 2019).”

Muendlein et al. (2019) developed a real-time PCR protocol for the detection of the LCT-13910C>T variant from whole blood samples. Lactose tolerance in adults is known to be strongly associated with the genetic variant LCT-13910C>T, which lies near the lactose encoding gene. Results from real-time PCR were compared to those from Sanger sequencing. A total of 105 whole blood samples were analyzed. When compared to Sanger sequencing, the real-time PCR protocol was determined to be a reliable method for the detection of the LCT-13910C>T (Muendlein et al., 2019).

Guidelines and Recommendations

American Academy of Pediatrics (AAP) (Heyman, 2006)

The AAP published guidelines (Heyman, 2006) on the evaluation of Lactose Intolerance in Infants, Children and Adolescents which recommend:

“Children with suspected lactose intolerance can be assessed clinically by dietary lactose elimination or by tests including noninvasive hydrogen breath testing or invasive intestinal biopsy determination of lactase (and other disaccharidase) concentrations. Treatment consists of use of lactase-treated dairy products or oral lactase supplementation, limitation of lactose-containing foods, or dairy elimination... If dairy products are eliminated, other dietary sources of calcium or calcium supplements need to be provided.”

The AAP also reported that “Recent studies suggest that in the future, genetic testing may be useful for identifying individuals at increased risk of lactase deficiency and consequent diminished bone mineral density, potentially allowing early intervention with dietary manipulation or nutrient supplementation.”

This statement was reaffirmed in 2012.

Genetic Testing for Lactase Insufficiency AHS – M2080

American College of Gastroenterology (ACG) (ACG, 2012)

The ACG has a webpage focused on lactose intolerance in children. Regarding diagnoses, the ACG states that “Lactose intolerance is diagnosed by a simple test called a hydrogen breath test (ACG, 2012).” Genetic testing was not mentioned.

Applicable Federal Regulations

A search for “lactose” on the FDA website on March 24, 2020, yielded no results for the genetic testing of lactose intolerance (FDA, 2019). Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81400

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

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Genetic Testing for Lactase Insufficiency AHS – M2080

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Genetic Testing for Lactase Insufficiency AHS – M2080

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Specialty Matched Consultant Advisory Panel review 7/2019

Medical Director review 7/2019

Specialty Matched Consultant Advisory Panel review 7/2020

Medical Director review 7/2020

Policy Implementation/Update Information

- 1/1/2019 BCBSNC will not provide coverage for genetic testing for lactase insufficiency because it is considered investigational for the use of targeted mutation analysis of -13910 C>T. BCBSNC does not provide coverage for investigational services or procedures. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (jd)

Genetic Testing for Lactase Insufficiency AHS – M2080

- 8/13/2019 Specialty Matched Consultant Advisory Panel review 7/2019. Medical Director review 7/2019. (jd)
- 9/10/2019 Reviewed by Avalon 2nd Quarter 2019 CAB. Minor revision to Description section. Added the following to the Policy Statement as investigational: “**and genetic testing of the LCT gene and/or MCM6 gene**”. Added second statement to the When Not Covered section: “**Genetic testing of the LCT gene and/or MCM6 gene for lactose intolerance and/or lactase insufficiency is considered investigational.**” Policy guidelines updated to support additional investigational indication. Billing/Coding section updated, removing code table. References updated. Policy noticed 9/10/2019 for effective date of 11/12/2019. Medical Director review 8/2019. (jd)
- 7/28/20 Reviewed by Avalon 2nd Quarter 2020 CAB. Related policies added. Policy guidelines and references updated. Specialty Matched Consultant Advisory Panel review 7/2020. Medical Director review 7/2020. (jd)

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