Genetic Testing for Lactase Insufficiency AHS – M2080

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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)

***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.

Policy Guidelines

Background
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The disaccharide 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 (Intiaz 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, 2018).

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 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).
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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., 2016a).

Clinical Validity and Utility

Marton et al 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, Xue, & Szilagyi, 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 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 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. They also stated that genetic tests will be negative in patients with secondary
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causes of lactase deficiency and that no information about clinical symptoms lactose intolerance will be obtained during testing (Misselwitz et al., 2013).

Brasen et al (2017) genotyped 3395 routine samples using real-time 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. They 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).”

Guidelines and Recommendations

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.”

They 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.

Applicable Federal Regulations

A search for “lactose” on the FDA website on February 27, 2019, 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.
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Scientific Background and Reference Sources


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Specialty Matched Consultant Advisory Panel review 7/2019

Medical Director review 7/2019

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)


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)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.