BlueCross BlueShield of North Carolina

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Corporate Medical Policy

Genetic Testing for Lactase Insufficiency AHS – M2080

File Name:	genetic_testing_for_lactase_insufficiency
Origination:	01/01/2019
Last CAP Review:	N/A
Next CAP Review:	01/01/2020
Last Review:	01/01/2019

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 (Levitt, Wilt, & Shaukat, 2013).

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., 2016)

******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. 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.

Policy Guidelines

Literature Review

The disaccharide lactose consists of galactose bound to glucose and is the main source of calories from mammalian milk. Intestinal absorption of lactose requires hydrolysis by the enzyme lactase, usually secreted by the microvilli of the small intestine. The ability to digest lactose during the

period of breast-feeding is essential; congenital lactase deficiency is fatal if not recognized very early after birth.

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 a dominant Mendelian trait(Enattah et al., 2002). 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(Sun et al., 2007; 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).

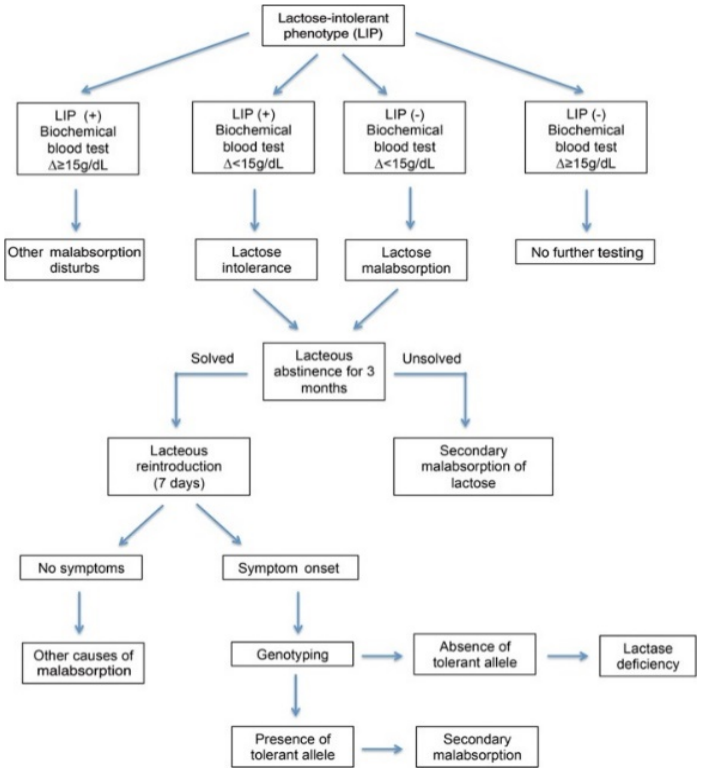
Lactase deficiency (LD) is defined as markedly reduced brush-border lactase activity relative to the activity observed in infants (Deng et al., 2015). Continued dairy consumption despite low expression of lactase results in unabsorbed lactose being present in the intestinal tract (lactose malabsorption (LM)), which can lead to symptoms of lactose intolerance (LI) in susceptible individuals (Gasbarrini et al., 2009).

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(Magge & Lembo, 2012; Shepherd, Lomer, & Gibson, 2013) are readily fermented by the colonic microbiome leading to production of short chain fatty acids and gas (mainly hydrogen (H_2), carbon dioxide (CO_2), and methane (CH_4)). Less often it can present with nausea or constipation and a range of systemic symptoms, including headaches, fatigue, loss of concentration, muscle and joint pain, mouth ulcers, and urinary difficulties(Campbell, Wann, & Matthews, 2004; Matthews & Campbell, 2000); however, it is unclear whether these atypical 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., 2016). 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 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. 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., 2016; Usai-Satta, Scarpa, Oppia, & Cabras, 2012).

	H_2-Breath Test [17,45]	Lactose Tolerance Test [46]	Genetic Test [3,12]	Lactase Activity at Jejunal Brush Border [43,44]
Test principle	Increase of H_2 in respiratory air after lactose challenge	Increase of blood sugar after lactose challenge	Genetic-13910C/T polymorphism	Enzymatic activity of lactase enzyme in biopsy sample
Cut off	>20 ppm within 3 h	<1.1 mmol/L within 3 h	C:C13910 lactase non-persistence	<17–20 IU/g
Availability	Good	Excellent	Variable	Rare
False positives (incorrect diagnosis)	Rapid GI-transit, small-intestinal bacterial overgrowth	Rapid GI-transit, impaired glucose tolerance	Rare (<5%) in Caucasians	Probably rare
False negatives malabsorption wrongly excluded	Non-H_2-producers. Full colonic adaptation	Fluctuations in blood sugar	All causes of secondary lactose malabsorption	Patchy enzyme expression
Secondary causes	Cannot be excluded, kinetic of H_2-increase can be suggestive	Cannot be excluded	Cannot be excluded	Can be excluded (histopathology at same procedure)
Symptom assessment	Possible	Possible	Not possible	Not possible
Comment	Method of choice for assessment of lactose malabsorption and intolerance	Rarely performed due to inferior sensitivity and specificity	Definitive in Caucasians. Less in other populations. Not suitable in secondary lactase deficiency.	Reference standard for detection of lactase deficiency (primary or secondary)
Cost	Low	Lowest	High	Highest

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). Figures from (Deng et al., 2015) (Ponte et al., 2016)



Clinical Validity and Utility

Montgomery et al (Montgomery, Grand, & Buuler, 2017) stated that "C/C (-13910) genotype has a sensitivity and specificity for lactase non-persistence of 93 and 100 percent, respectively, which is comparable to the accuracy of the lactose tolerance test and breath hydrogen tests. However, people with the genotype T/C (-13910) can be lactase persistent or non-persistent. In addition, the test is expensive and may not be useful for patients of African origin."

Baffour-Awuah et al (Baffour-Awuah et al., 2015) 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."

Misselwitz et al (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. They also stated that genetic tests will be negative in patients with secondary causes of lactase deficiency. Importantly, no information about clinical symptoms lactose intolerance is obtained during testing.

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%."

No studies were found that outlined changes to patient management and improvement in clinical outcomes due to genetic testing. There is a lack of published evidence regarding the clinical utility of genetic testing for lactose intolerance.

Applicable Federal Regulations

This test is considered a laboratory developed test (LDT); developed, validated and performed by individual laboratories.

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.

Guidelines and Recommendations

Practice Guidelines and Position Statements

American Association for Pediatrics
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."

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

Code Number	PA Required	PA Not Required	Not Covered
84100	X		

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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on food choices. *Neurogastroenterology & Motility*, *27*(8), 1138-1146. doi:10.1111/nmo.12602

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)