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Medical Policy Manual

Topic: Genetic Testing for Lactase Insufficiency

Section: Genetic Testing

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Genetic testing of adults with suspected lactase insufficiency is proposed as an alternative to current diagnostic practices. Studies have demonstrated a tight correlation between a single nucleotide polymorphism (SNP) -13910 C>T upstream of the gene coding for the enzyme lactase and lactase insufficiency in persons of European ancestry. Currently, two indirect tests of lactose digestion, the hydrogen breath test (HBT) and lactose tolerance blood test (LTT), are the most preferred diagnostic tests for confirmation of lactase insufficiency.

Background

The predominant carbohydrate in milk is the disaccharide lactose consisting of the simple sugars glucose and galactose. The brush-border enzyme lactase hydrolyzes lactose into its monosaccharide components that are absorbable by the intestinal mucosa. Except for rare instances of congenital hypolactasia, most infants are able to produce lactase with enzyme levels highest at birth. Sometime after weaning in the majority of 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 two groups emerge: a group with insufficient levels of lactase activity (primary hypolactasia or lactase

non-persistence) and a group that retains the infant level of lactase activity through adulthood (lactase-persistence).[3] The ethnic groups with the highest rates of lactase insufficiency are Asian, Native American and Blacks with the lowest rates in people of northern European origin. (Table 1)

Table 1. Prevalence of Lactase Insufficiency by Country or Ethnicity[4]

Population	Lactase Insufficiency*%
Northern Europeans	2 to 15%
American Whites	6 to 22%
Central Europeans	9 to 23%
Northern Indians	20 to 30%
Southern Indians	60 to 70%
Hispanics	50 to 80%
Ashkenazi Jews	60 to 80%
Blacks	60 to 80%
American Indians	80 to 100%
Asians	95 to 100%

*Identified through HBT or LTT

Problems with the absorption of lactose can be described in several terms:

- Lactase insufficiency (lactase non-persistence 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 with a homozygous lactase persistence genotype (T/T) lactase levels are approximately 10-times higher than for the lactase insufficient genotype (C/C) with heterozygous individuals (C/T) showing intermediate levels.[6] These heterozygous individuals may experience symptoms of lactose intolerance when ingesting quantities of lactose greater than their intermediate level of lactase can digest.
- Lactose malabsorption – indicates that a sizable fraction of lactose is not able to be absorbed in the small bowel and is delivered to the colon. Malabsorption is tested by HBT or LTT.[5]
- Lactose intolerance – indicates that lactose malabsorption causes gastrointestinal symptoms. There is no genetic test for lactose intolerance and demonstration of lactose intolerance requires patients to self-report symptoms after lactose ingestion (Table 2). Diagnosis of lactose intolerance is highly susceptible to the placebo effect and studies should appropriately conduct a blinded lactose challenge with an indistinguishable placebo.[3] A meta-analysis by Jellema and colleagues indicated that no specific patient complaint could predict lactose malabsorption with sensitivity and specificity ranging from 0-90% and 18-96% for the most common lactose intolerance symptoms.[7] Similarly, patient self-reported milk tolerance was also not found to be accurate in predicting lactose malabsorption with sensitivity and specificity ranging from 30-70% and 25-87% respectively.[7]

Table 2. Symptoms of Lactose Intolerance[2]

Gut-related symptoms	% of total patients who experience symptom

Abdominal pain	100
Gut distention	100
Borborygmi	100
Flatulence	100
Diarrhea	70
Constipation	30
Nausea	78
Vomiting	78
Systemic symptoms	
Headache and light headedness	86
Loss of concentration and poor short-term memory	82
Long-term severe tiredness	63
Muscle pain	71
Joint pain and/or swelling	71
Allergy (eczema, pruritus, rhinitis, sinusitis, asthma)	40
Heart arrhythmia	24
Mouth ulcers	30
Increased frequency of micturition	<20
Sore throat	<20

Lactase insufficiency is a common condition which occurs in approximately (70%) of persons after weaning.[8] An insufficiency of lactase results in the malabsorption of lactose, 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, the demonstration of lactose malabsorption does not necessarily indicate that an individual will be symptomatic. Many variables determine if a person who malabsorbs lactose develops symptoms, including: 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 the 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 fraction of those who are lactase insufficient. In addition, lactose malabsorption may be secondary (secondary hypolactasia) to an acquired condition such as: small bowel bacterial overgrowth, infectious enteritis, mucosal damage from celiac disease, inflammatory bowel disease, antibiotics, gastrointestinal surgery, short bowel syndrome, radiation enteritis or other conditions which may lead to reduction of lactase expression in the small intestine.[6]

Clinical Diagnosis of Lactase Insufficiency

Mucosal biopsy of the duodenum followed by biochemical lactase assay to directly measure lactase activity is the reference standard for diagnosis of lactase insufficiency. This approach may also exclude other causes of secondary lactose malabsorption through endoscopy. However, this approach is limited in utility 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 level are the hydrogen breath test (HBT) and lactose tolerance blood test (LTT) which measure lactose malabsorption. Because lactose malabsorption is nearly always attributable to lactase insufficiency, this can typically be imputed from measurements of lactose malabsorption.[3]

The HBT measures the amount of hydrogen exhaled by gas chromatography for up to 3 hours after ingesting 25-50 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 0.31–2.5 mL/min is indicative of bacterial fermentation from the malabsorbed lactose. A negative HBT can exclude lactose malabsorption as the cause of symptoms, and a positive result indicates that the symptoms may be attributable to ingestion of lactose.[3] The following factors are associated with a rise in breath hydrogen and may cause false-positive results if present at 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 LTT measures blood glucose increase over time with blood drawn at 15, 30, 60, and 90 minutes after ingesting a 25-50 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 a rise in 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 of Lactase Insufficiency

Enattah and colleagues identified the first DNA variant to control transcription of lactase in 2002.[10] This polymorphism, -13910 C>T, is located in a noncoding region of the MCM6 gene that is upstream of the lactase gene (LCT or lactase-phlorizin hydrolase). The less common T allele has been associated with lactase persistence and has demonstrated an autosomal dominant pattern of inheritance. This polymorphism is thought to be related to the domestication of animals during the last 10,000-12,000 years, and persons with the C/C genotype have been shown to be strongly associated with lactase

insufficiency phenotype in Caucasians. Other polymorphisms have been identified in the same MCM6 regulatory region which are associated with additional ethnic groups (such as Africans and Arabs), but these have not been as commonly observed and to date no commercially available testing kits have incorporated these polymorphisms.[6]

Prometheus's LactoType® is a commercially available PCR-based test that assesses the most common lactase non-persistence variant, -13910 C>T, in patients with suspected lactose intolerance. Demonstration of the C/C genotype can be used as indirect evidence of lactase insufficiency and lactose malabsorption.

Treatment of Lactase Insufficiency

The goal of treatment should be to ensure adequate nutrients important for skeletal health.[1] Dietary adjustment to restrict the consumption of foods containing lactose is the principal form of therapy for patients with lactase insufficiency. However, even lactose maldigesters can usually tolerate small amounts of lactose (12 g/day) with no or minimal symptoms. Lactase enzyme preparations are available for symptom relief but may not be effective in all patients.

Regulatory Status

No U.S. Food and Drug Administration (FDA)-cleared genotyping tests were found. Thus, genotyping is offered as a laboratory-developed test. Clinical laboratories may develop and validate tests in-house ("home-brew") and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA).The laboratory offering the service must be licensed by CLIA for high-complexity testing.

MEDICAL POLICY CRITERIA

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

SCIENTIFIC EVIDENCE

Validation of the clinical use of any genetic test focuses on 3 main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. The clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

The focus of this review is on evidence related to the ability of test results to:

- Guide decisions in the clinical setting related to either treatment, management, or prevention, and

- Improve health outcomes as a result of those decisions.

Literature Appraisal

Analytical and Clinical Validity

No studies were identified specifically regarding the analytical sensitivity and specificity for polymerase chain reaction (PCR) sequencing of LCT -13910 C>T polymorphism; however, many reports on the diagnosis of lactase insufficiency by PCR mutation analysis of -13910 C>T have been published. Reports which assess the agreement between genotyping and HBT, LTT or biopsy are presented in Table 3. Eighteen studies compared genotyping of SNP -13910 C>T to HBT and found a sensitivities and specificities ranging from 71-100% and 46-100%, respectively. Five studies compared genotyping to LTT with sensitivity and specificity ranging from 85-100% and 87-95%, respectively. Heterogeneity in study population, dose of lactose given in HBT/LTT, and age of participants contributed to the wide range of observed sensitivities and specificities. A direct comparison of these tests is prohibited because no studies were identified that compared genotyping and HBT/LTT to the gold standard of biopsy. Indirect comparison is not possible due to the small number of studies comparing genotyping, HBT, or LTT to biopsy.

It is to be expected that there is not complete agreement between genotyping for lactase insufficiency and indirect tests of lactose malabsorption as these tests do not measure the same parameters. LTT and HBT are intended to diagnosis lactose malabsorption that can be caused by reasons 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. DiStefano and colleagues found that the overall kappa value for the agreement of HBT and genotyping was .74, but for those younger than and older than 30 years of age, the kappa values were .56 and 1, respectively ($p<0.005$).

In addition, the SNP -13910 C>T is not the only MCM6 polymorphism implicated in regulating transcription of the LCT gene. A study by Eadala and colleagues recruited patients with irritable bowel disease along with healthy control patients and found that while the C/C genotype was strongly associated with experiencing symptoms of lactose intolerance following HBT, there was a high proportion of lactose sensitivity in C/T and T/T genotype patients as well.[11] A study by Mendoza-Torres and colleagues found a low (46%) specificity when comparing HBT to genotyping. The authors attributed this finding to the genetic heterogeneity of the Colombian and Caribbean population studied and recommended against using genotyping to assess lactase insufficiency in this population.[12] These results suggest that unmeasured genetic variation may help explain lactase insufficiency.

Table 3. Sensitivity and Specificity of Analysis of the Genotyping Compared with HBT, LTT, and Intestinal Biopsy

Author, Year, Country	N	Sensitivity (95% CI)	Specificity (95% CI)
Targeted mutation analysis of SNP -13910 C>T results compared with hydrogen breath test (HBT)			
Gugatschka, 2005, Austria [13]	51	90 (73-98)	95 (76-100)
Buning, 2005, Germany[14]	166	98 (93-100)	83 (71-91)
Hogenauer, 2005, Austria[9]	123	97 (86-100)	86 (77-93)

Bulhoes, 2007, Brazil[15]	20	90 (55-100)	100 (69-100)
Schirru, 2007, Italy[16]	84	84 (72-93)	96 (81-100)
Bernardes, 2007, Brazil[17]	147	76 (59-89)	100 (40-100)
Szilagyi, 2007, Canada[18]	30	93 (68-100)	80 (52-96)
Kerber, 2007, Austria[19]	120	97 (86-100)	72 (61-95)
Mattar, 2008, Brazil[20]	50	96 (82-100)	100 (85-100)
Krawcyk, 2008, Germany[21]	58	100 (78-100)	95 (84-99)
Mottes, 2008, Italy[22]	112	71 (60-80)	83 (61-95)
Waud, 2008, Wales[23]	200	100 (88-100)	64 (57-71)
DiStefano, 2008, Italy[24]	32	88 (70-98)	100 (54-100)
Nagy, 2009, Hungary[25]	186	77 (68-85)	94 (87-98)
Szilagyi, 2009, Canada[26]	57	97 (83-100)	93 (76-99)
Babu, 2010, India[27]	153	87 (80-93)	97 (85-100)
Pohl, 2010, Germany[28]	194	90 (80-96)	98 (94-100)
Mendoza-Torres, 2011, Columbia[12]	126	97	46
Morales, 2011, Chile[29]	51	96.3	87.5
Targeted mutation analysis of SNP -13910 C>T results compared with blood lactose tolerance test (LTT)			
Nilsson, 2004, Sweden[30]	35	100	88
Gugatschka, 2005, Austria[13]	46	85	90
Ridefelt, 2005, Canada[31]	51	90	95
Szilagyi, 2007, Canada[18]	30	93	87
Babu, 2010, India[27]	153	97	87
Targeted mutation analysis of -13910 C>T results compared with biopsy determined lactase level			
Rasinpera, 2004, Finland[32]	329	--	--
	<5 Years: 109	80	65.4
	6-11 Years: 142	94.6	81.9
	≥12 Years: 78	93.3	100
Nilsson, 2004, Sweden[30]	35	100	88
Kuchay, 2011, India[33]	176	--	--
	Children >5:	96	78.9
	Children >8:	97.2	100

There is some heterogeneity in how the HBT/LTT test was conducted (e.g. using 25 g of lactose or 50 g) and the population tested (e.g. inclusion of children or the racial and ethnic composition of the study population).

A meta-analysis by Marton et al. assessed the diagnostic accuracy of the LTT and HBT tests compared to genotyping for the polymorphism -13910 C>T for prediction of lactase insufficiency phenotype.[34] Seventeen studies evaluated HBT and 5 evaluated LTT. The overall sensitivity and specificity of the HBT was 88% (95% confidence interval [CI]: 85-90%) and 85% (95% CI: 82-87%), respectively. Both sensitivity and specificity showed high heterogeneity (I2 78% and 87%) and the authors detected a potential for publication bias within their included studies. LTT overall sensitivity was 94% (95% CI: 90-97%) with a specificity of 90% (95% CI: 84 – 95%). No significant heterogeneity was observed for the sensitivity and specificity of the LTT.

Clinical Utility

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

Lactase insufficiency is the normal phenotype for most adults, and a confirmatory diagnosis with HBT, LTT, or genotyping is generally not necessary. Empiric diagnosis by dietary restriction is adequate in most circumstances as this is the primary treatment for lactase insufficient patients. Patients who achieve satisfactory symptom control following dietary modifications do not require further diagnostic testing. For the majority of patients who do not achieve symptom control following dietary modifications, testing is indicated for the presence of other conditions that can cause symptoms similar to lactase deficiency.

Clinical Practice Guidelines

No evidence-based clinical practice guidelines were identified which recommend genetic testing for prediction of lactase insufficiency, for any condition.

Summary

There is no current treatment for lactase insufficiency, and management involves dietary restriction and palliation of lactose intolerance symptoms, which is often prescribed in the absence of confirmation of lactase insufficiency with HBT, LTT or genotyping. Additionally, there is insufficient evidence that genetic testing to determine lactase insufficiency would affect patient management or improve health outcomes. Therefore, the use of targeted mutation analysis of -13910 C>T for the prediction of lactase insufficiency is considered investigational.

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CROSS REFERENCES

None

CODES	NUMBER	DESCRIPTION
CPT	81400	Molecular pathology procedure, Level 1
HCPCS	None	