Protocol

Genetic Testing for Lactase Insufficiency

(20494)

Medical Benefit		**Effective Date**: 10/01/13	**Next Review Date**: 07/18
Preauthorization	No	**Review Dates**: 07/13, 07/14, 07/15, 07/16, 07/17	

This protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Description

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.

Summary of Evidence

Studies have demonstrated a high correlation between a single nucleotide polymorphism, -13910 C>T upstream of the gene encoding the enzyme lactase, and lactase insufficiency in persons of European ancestry. Studies in white populations report a high degree of agreement for the diagnosis of lactase insufficiency between genotyping and both hydrogen breath test (HBT) and lactose tolerance blood test (LTT).

Genetic testing has the potential advantage of sparing patients the discomfort of fasting and experiencing symptoms of lactose intolerance during the administration of HBT or LTT. Genotyping also may have additional utility in the diagnosis of secondary hypolactasia.

However, there is no current treatment for lactase insufficiency, and management involves dietary restriction and palliation of lactose intolerance symptoms. Therefore, an empiric 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 there is insufficient evidence that the assessment of the genetic etiology of lactose intolerance would affect patient management or improve clinical outcomes. The use of targeted mutation analysis of -13910 C>T for the prediction of lactase insufficiency is therefore considered investigational.

Policy

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

Background

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.[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 two 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 (lactase-persistence).[3] 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 (see Table 1).

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

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 (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.[5] 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 10 times higher than in those who are homozygous lactase insufficient (C/C); heterozygous persons (C/T) have intermediate lactase activity levels.[6] 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 indicates that a large portion of lactose cannot 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; 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.[3] 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.[7] 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.[7]

Table 2. Symptoms of Lactose Intolerance[2]

Symptoms	Percent 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

Lactase insufficiency is common, occurring in approximately (70%) of persons after weaning.[8] 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.[9] 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.[6]

Clinical Diagnosis of Lactase Insufficiency

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, this typically can be imputed from assessment of lactose malabsorption.[3]

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.[3] 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 LTT 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 under-going 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

In 2002, Enattah et al identified the first DNA variant to control transcription of lactase.[10] This polymorphism, -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 polymorphism 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 polymorphisms in the same *MCM6* regulatory region are associated with other ethnic groups (e.g., Africans, Arabs), but the prevalences of these vary geographically[6, 11] and to date, no commercially available testing kits have incorporated these polymorphisms.

Prometheus's *Lacto*TYPE® is a commercially available polymerase chain reaction–based test that assesses the most common lactase nonpersistence variant, *MCM6* -13910 C>T, in patients with suspected lactose intolerance. Fulgent Clinical Diagnostics Lab 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 of Lactase Insufficiency

The goal of treatment should be to ensure adequate nutrition for skeletal health.[1] 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.

Regulatory Status

No U.S. Food and Drug Administration–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 general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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41. National Government Services, Inc. (Primary Geographic Jurisdiction - Illinois, New York - Entire State, Connecticut, Massachusetts, Maine, New Hampshire, Rhode Island, Vermont, Wisconsin, Minnesota) Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000), Revision Effective Date For services performed on or after 02/01/2017.