# *Genetic Testing for Lactase Insufficiency*

**Effective**: April 1, 2025

**Next Review:** January 2026
**Last Review:** February 2025

## 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, such as the hydrogen breath test (HBT) and lactose tolerance blood test (LTT).

## MEDICAL POLICY CRITERIA

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

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

## CROSS REFERENCES

None

## 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.

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.[4] 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.[5] 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.[4]

- 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 (2010) indicated that no specific patient complaint could predict lactose malabsorption with sensitivity and specificity ranging from 0 to 90% and 18 to 96% for the most common lactose intolerance symptoms.[6] Similarly, patient self-reported milk tolerance was also not found to be accurate in predicting lactose malabsorption with sensitivity and specificity ranging from 30 to 70% and 25 to 87% respectively.[6]

**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 |

| Gut-related symptoms | % of total patients who experience symptom |
|---|---|
| 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.[7] 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.[8] 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.[5]

## 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 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 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 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 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 (2002) identified the first DNA variant to control transcription of lactase.[9] This variant, -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 to 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 prevalences of these vary geographically and to date no commercially available testing kits have incorporated these polymorphisms.[5]

Prometheus's LactoType® is a commercially available polymerase chain reaction (PCR)-based test that assesses the most common lactase non-persistence variant, -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 nutrients important for skeletal health. Dietary adjustment to restrict the consumption of foods containing lactose is the principal form of therapy for patients with lactase insufficiency. However, even lactose maldigestors 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.

## EVIDENCE SUMMARY

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

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant 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.

### Analytical and Clinical Validity

According to the Genetic Testing Registry, analytical sensitivity of next-generation sequencing and deletion/duplication analysis of *MCM6* exceeds 98%. The group also reported that analytical specificity and accuracy are 96% and 97% respectively.[10] No studies were identified regarding the analytical sensitivity and specificity for PCR sequencing of the *LCT* -13910 C>T polymorphism; however, many reports on the diagnosis of lactase insufficiency by PCR variant 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. There were 20 studies that compared genotyping of SNP -13910 C>T to HBT and found sensitivities and specificities ranging from 71 to 100% and 46 to 100%, respectively. Five studies compared genotyping to LTT with sensitivity and specificity ranging from 85 to 100% and 87 to 95%, respectively. One study by Enko (2014) compared genotyping to a hydrogen/methane breath test (H/MBT), which may be more sensitive than HBT, and reported Cohen's kappa statistic of 0.44, indicating moderate agreement.[11] 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 was prohibited as 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. Di Stefano (2009) found that the overall kappa value for the agreement of HBT and genotyping was 0.74, but for those younger than and older than 30 years of age, the kappa values were 0.56 and 1, respectively ($p<0.005$).[12]

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 (2011) 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.[13] A study by Mendoza-Torres 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.[14] Similarly, in 2015, Santonocito, found a similar proportion (~80%) of homozygous genotypes for lactase non-persistence among 1,426 patients with gastrointestinal symptoms and 1,000 healthy volunteers in south central Italy.[15] 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 variant analysis of SNP -13910 C>T results compared with hydrogen breath test (HBT)** | | | |
| Gugatschka, 2005, Austria[16] | 51 | 90 (73 to 98) | 95 (76 to 100) |
| Buning, 2005, Germany[17] | 166 | 98 (93 to 100) | 83 (71 to 91) |
| Hogenauer, 2005, Austria[8] | 123 | 97 (86 to 100) | 86 (77 to 93) |
| Bulhoes, 2007, Brazil[18] | 20 | 90 (55 to 100) | 100 (69 to 100) |
| Schirru, 2007, Italy[19] | 84 | 84 (72 to 93) | 96 (81 to 100) |
| Bernardes, 2007, Brazil[20] | 147 | 76 (59 to 89) | 100 (40 to 100) |
| Szilagyi, 2007, Canada[21] | 30 | 93 (68 to 100) | 80 (52 to 96) |
| Kerber, 2007, Austria[22] | 120 | 97 (86 to 100) | 72 (61 to 95) |
| Mattar, 2008, Brazil[23] | 50 | 96 (82 to 100) | 100 (85 to 100) |
| Krawcyk, 2008, Germany[24] | 58 | 100 (78 to 100) | 95 (84 to 99) |
| Mottes, 2008, Italy[25] | 112 | 71 (60 to 80) | 83 (61 to 95) |
| Waud, 2008, Wales[26] | 200 | 100 (88 to 100) | 64 (57 to 71) |
| DiStefano, 2008, Italy[12] | 32 | 88 (70 to 98) | 100 (54 to 100) |
| Nagy, 2009, Hungary[27] | 186 | 77 (68 to 85) | 94 (87 to 98) |

| Author, Year, Country | N | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|
| Szilagyi, 2009, Canada[28] | 57 | 97 (83 to 100) | 93 (76 to 99) |
| Babu, 2010, India[29] | 153 | 87 (80 to 93) | 97 (85 to 100) |
| Pohl, 2010, Germany[30] | 194 | 90 (80 to 96) | 98 (94 to 100) |
| Mendoza-Torres, 2011, Columbia[14] | 126 | 97 | 46 |
| Morales, 2011, Chile[31] | 51 | 96.3 | 87.5 |
| Buzás, 2016, Hungary[32] | 496 | 96.6 | 80.4 |
| **Targeted variant analysis of SNP -13910 C>T compared with H/MBT** | | | |
| Enko, 2005, Austria[11] | 263 | 79 | 87 |
| **Targeted variant analysis of SNP -13910 C>T results compared with blood lactose tolerance test (LTT)** | | | |
| Nilsson, 2004, Sweden[33] | 35 | 100 | 88 |
| Gugatschka, 2005, Austria[16] | 46 | 85 | 90 |
| Ridefelt, 2005, Canada[34] | 51 | 90 | 95 |
| Szilagyi, 2007, Canada[21] | 30 | 93 | 87 |
| Babu, 2010, India[29] | 153 | 97 | 87 |
| **Targeted variant analysis of -13910 C>T results compared with biopsy determined lactase level** | | | |
| Rasinpera, 2004, Finland[35] | 329<br><5 Years: 109<br>6 to 11 Years: 142<br>≥12 Years: 78 | --<br>80<br>94.6<br>93.3 | --<br>65.4<br>81.9<br>100 |
| Nilsson, 2004, Sweden[33] | 35 | 100 | 88 |
| Kuchay, 2011, India[36] | 176<br>Children >5:<br>Children >8: | --<br>96<br>97.2 | --<br>78.9<br>100 |
| Mattar, 2013, Brazil[37] | 32 | 100 | 48 |

- CI; confidence interval; HBT: hydrogen breath test; H/MBT: hydrogen methane breath test; LTT: lactose tolerance blood test; NR: not reported; SNP: single nucleotide polymorphism.
- There was 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, 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.[38] 17 studies evaluated HBT and five evaluated LTT. The overall sensitivity and specificity of the HBT was 88% (95% confidence interval [CI] 85 to 90%) and 85% (95% CI 82 to 87%), respectively. Both sensitivity and specificity showed high heterogeneity ($I^2$, 78% and 87%) and the authors detected a potential for publication bias within their included studies. LTT overall sensitivity was 94% (95% CI 90 to 97%) with a

specificity of 90% (95% CI 84 to 95%). No significant heterogeneity was observed for the sensitivity and specificity of the LTT.

**Clinical Utility**

No studies were identified which demonstrated 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.

## PRACTICE GUIDELINE SUMMARY

No evidence-based clinical practice guidelines were identified with recommendations regarding genetic testing for prediction of lactase insufficiency for any condition.

## SUMMARY

There is not enough research to show that genetic testing improves health outcomes for people that may have lactase insufficiency. There are no clinical guidelines based on research that recommend this testing for people with any condition. Therefore, the use of targeted variant analysis of -13910 C>T for the prediction of lactase insufficiency is considered investigational.

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## CODES

| Codes | Number | Description |
|---|---|---|
| CPT | 81400 | Molecular pathology procedure, Level 1 |
| HCPCS | None | |

***Date of Origin:*** *January 2014*