Genetic testing for maple syrup urine disease

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Policy contains: Branched-chain ketoaciduria, genetic testing, maple syrup urine disease, mutation.

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Coverage policy

Genetic testing (for mutations in the *BCKDHA, BCKDHB* and *DBT* genes) for screening and diagnosis of maple syrup urine disease (branched-chain ketoaciduria) is clinically proven and, therefore, may be medically necessary when one of the following criteria are met (National Organization for Rare Diseases, 2020):

- There is a family history of an affected sibling with the condition.
- The newborn or infant has symptoms of the condition, and newborn screening is unavailable or fails to detect maple syrup urine disease.

All of the following criteria must also be met:

- The test is ordered and interpreted by a trained professional.
- The result of the test will directly impact management of the patient and/or guardian.
- The test is an analytically and clinically valid test (i.e., supported by peer-reviewed published research).
- Women with positive screening test results are offered further counseling and testing.

Limitations

Repeated uses of genetic testing for diagnosis and screening of maple syrup urine disease are not clinically proven, and therefore, not medically necessary.

Alternative covered services

Routine patient evaluation and management by a network health care provider, including invasive prenatal diagnostic tests with amniocentesis or chorionic villus sampling.

Background

Newborn screening includes a group of tests performed via a heel prick and urine sampling at birth to rule out certain metabolic, physical or functional conditions (Mujamammi, 2022). Maple syrup urine disease is an amino acid disorder, a rare genetic condition that occurs between 1 in 86,800 and 1 in 185,000 live births (Bodamer, 2023; Mujamammi, 2022). While most cases are considered “classic,” 20% are not; and are designated as intermittent or intermediate variants (Pode-Shakked, 2020).

The condition has an annual incidence of about 18 new cases in the U.S. A review of over 21 million births in nine U.S. states from 2001-2013 estimated one case in every 220,219 births, based on 91 births with the disorder (Chapman, 2018). It is more common in certain populations, such as Old Order Mennonites (one in 200 births) and Ashkenazi Jews (one in 26,000) (Bodamer, 2023; National Organization for Rare Diseases, 2020).

The disease is characterized as an amino acid metabolic disorder similar to phenylketonuria. where the body is unable to break down specific amino acids or assist in the excretion of nitrogen; or process certain protein building blocks (amino acids) for use (Mujamammi, 2022). It is marked by poor feeding, vomiting, lethargy, abnormal movements, and developmental delays.

The progression of the disease events over time in untreated newborns is characterized by:

- 12-24 hours: Elevated branched-chain amino acids and generalized disturbance of amino acid concentration ratios in blood; maple syrup odor detected in cerumen.
- 2-3 days: Early, non-specific signs of metabolic intoxication (irritability, hypersomnolence, anorexia), plus presence of branched-chain alpha-ketoacids, acetoacetate, and beta-hydroxyburyrate in urine
- 4-6 days: Worsening lethargy due to encephalopathy, apnea, opisthotonos, and reflexive “fencing” or “bicycling” movements; maple syrup odor apparent in urine.
- 7-10 days: Severe intoxication culminating in critical cerebral edema, coma, and central respiratory failure (Strauss, 2020).

Each parent of children with maple syrup urine disease carries a single non-working gene, but rarely have the condition. When both parents are carriers, there is a 25% chance in each pregnancy that the child will develop maple syrup urine disease (Newborn Screening Info, 2023).

Screening for maple syrup urine disease was first conducted in 1964 (Blackburn, 2017). Each of the 50 states now requires all newborns be screened for 34 diseases, including maple syrup urine disease (University of Rochester, 2023). Testing is typically done using a blood sample, and tandem mass spectrometry, which can test for multiple diseases from one blood sample, can help with diagnosis (Blackburn, 2017; National Organization for Rare Disorders, 2020).

Screening for maple syrup urine disease can result in false positives from generalized aminoacidemia or hydroxyprolinemia, or false negatives for milder forms of the disorder. However, rapid follow up of positive newborn screening results limits the number of infants with severe clinical symptoms (Frazier, 2014).

Genetic testing, which can identify changes in the pair of genes that causes maple syrup urine disease, is another option. If a child has been diagnosed with maple syrup urine disease, indicating greater risk for the disorder for any siblings, genetic testing may be performed using chorionic villus sampling or amniocentesis (Newborn Screening Info, 2023).

Classic maple syrup urine disease is caused by known mutations in the *BCKDHA*, *BCKDHB*, and *DBT* genes at the 19q13.2, 6q14.1, and 1p21.2 loci, respectively. These genes encode proteins essential for breaking down branched-chain amino acids, although multiple less-widely attributed gene mutations may also be in play (Su, 2017). Individuals with intermediate maple syrup urine disease have a partial enzyme deficiency that only manifests intermittently; these individuals can experience severe metabolic intoxication and encephalopathy during periods of sufficient catabolic stress and protein breakdown.

Treatment of the disease includes lifelong dietary therapy to maintain acceptable amino acid levels in the body and immediate medical intervention for metabolic crises. In addition, a protein-restrictive diet with limited amounts of branched-chain amino acids is recommended, along with addition of the enzymes leucine, isoleucine, and valine. The sooner after birth/diagnosis that protein restriction is initiated, the more likely it is for the child to recover. Monitoring of infant symptoms and enzyme levels during treatment is essential (National Organization of Rare Diseases, 2020).

A study from southeast Pennsylvania, the site of a colony of Old Order Mennonites, assessed 184 residents with the disease (176 of whom were classified as severe) diagnosed over 30 years. Authors state the condition is “morbid and potentially fatal.” Even stringent dietary therapy is challenging to implement, fails to restore appropriate concentration relationships among circulating amino acids, and does not fully prevent cognitive and psychiatric disabilities (Strauss, 2020).

Findings

Clinical Guidelines:
The National Organizations for Rare Diseases endorses genetic testing for certain congenital conditions, including maple syrup urine disease, when 1) there is a family history of an affected sibling with the condition; 2) the newborn or infant has symptoms of the condition, and screening is unavailable or fails to detect the disease. These criteria are the basis for the coverage section on page one of this policy (National Organization for Rare Diseases, 2020).

The American College of Obstetricians and Gynecologists offers direction in its Committee Opinion (American College of Obstetricians and Gynecologists, 2023) concerning carrier screening for genetic conditions, including uncommon conditions, in the Ashkenazi Jewish population. Among the disease entities identified by the College that should be considered in this cohort for individual testing is maple syrup urine disease.

The Society of Obstetricians and Gynaecologists of Canada and the Canadian College of Medical Geneticists issued an opinion for reproductive genetic carrier screening (Wilson, 2016). This joint committee recommends that Ashkenazi Jewish carrier screening be offered when a positive family pedigree is elicited for one of the

conditions known to be present at an increased frequency in this population. Among these disorders is maple syrup urine disease, with a risk of one newborn with the disease for each 97 affected families.

Literature Review[VD1]:

Newborn Screening and Diagnosis:
Several studies have investigated the effectiveness of newborn screening and diagnosis for maple syrup urine disease. A systematic review identified 53 patients and eight false negatives from tandem mass spectrometry screening, while 51 cases were detected by other methods of screening amino acid concentrations (Stroek, 2020). Another study reviewed 2,200,000 California newborns screened from 2005-2009, revealing 17 cases, with three missed cases and two late-onset cases (Puckett, 2010). It was reported that screening was instituted in the United Kingdom following a pilot study that found 12 confirmed cases of rare conditions, including maple syrup urine disease, in just under 440,000 births (Hawkes, 2014). Among 83 Brazilian patients diagnosed between 1992 and 2011, only 3.6% were diagnosed before the onset of clinical manifestations, highlighting the need for improved public policies for diagnosis and treatment (Herber, 2015).

Molecular and Genetic Studies:
Molecular and genetic studies have been conducted to better understand maple syrup urine disease and improve diagnosis. A report on mutation analysis of three genes encoding the BCKD complex in 52 patients detected 25 disease-causing mutations and successfully carried out prenatal molecular genetic testing in 10 expectant mothers with affected children (Imitaz, 2017). Another study detected genes related to the disease in 22 of 24 patients, with mutations found in BCKDHB, BCKDHA, and DBT genes (Gupta, 2015). A comparison of polymerase chain reaction with DNA testing in 160 Old Order Mennonites found that DNA testing was more sensitive and reduced assay time for diagnosis from 12 to five hours (Carleton, 2010).

High-Risk Populations and Community Initiatives:
Maple syrup urine disease affects about one per 400 Amish and Mennonite infants, and community initiatives have been established to manage and screen high-risk populations. A management study of 68 Mennonite patients from the newborn period found that half were targeted diagnoses due to positive family history or carrier testing and managed as outpatients, while the remainder were diagnosed by newborn screening and hospitalized for an average of five days (Strauss, 2012). Testing for maple syrup urine disease and propionic acidemia was provided in a high-risk population through a community project in Wisconsin (Kuhl, 2017). A systematic review and meta-analysis estimated the birth prevalence of inherited metabolic disorders, including maple syrup urine disease, in England based on targeted screening with tandem mass spectrometry (Moorthie, 2014).

Clinical Features, Outcomes, and Genotype-Phenotype Correlations:
Studies have assessed the clinical features, neurological outcomes, and genotype-phenotype correlations in maple syrup urine disease patients. One study found that patients detected by screening remained asymptomatic, while those diagnosed by clinical symptoms experienced encephalopathy, higher leucine levels, and more hospitalizations; a good genotype-phenotype correlation was found, and four novel mutations were identified (Couce, 2015). Another study reported that 98.8% of Brazilian patients exhibited psychomotor or neurodevelopmental delay, attributed to delayed diagnosis and lack of specific public policies (Herber, 2015). Additional reports noted movement disorders, cognitive, attention, and mood disorders in adult patients (Carecchio, 2011; Muelly, 2013). While newborn screening allows for early detection of classic maple syrup urine disease, the intermittent type may go undetected and present later in life with various symptoms (Pode-Shakked, 2020).

In 2024, we reorganized the findings section of the policy. No new relevant literature was found or added to the policy.

References

On May 12, 2024, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “branched-chain ketoaciduria,” “genetic testing,” “maple syrup urine disease,””amino acid metabolic disorder,” and “mutation.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

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