Maple Syrup Urine Disease (MSUD): *BCKD* Complex Gene Deletion/Duplication

**Test Code:** NI  
**Turnaround time:** 2 weeks  
**CPT Codes:** 81228 x1

### Condition Description

Maple syrup urine disease (MSUD) is an organic aciduria that is caused by the inability to break down branch-chain amino acids, leucine, isoleucine, and valine. The resulting build-up of these amino acids results in vomiting, dehydration, severe metabolic acidosis, a characteristic maple syrup odor of the sweat and urine. MSUD is among the disorders tested for by newborn screening and is treatable by dietary modification.

MSUD affects between 1 in 125,000 and 1 in 300,000 people in the general population. MSUD is common in the Old Order Mennonite population of southeastern Pennsylvania, occurring in 1 in 760 live births. MSUD is inherited in an autosomal recessive manner, therefore the recurrence risk for carrier parents of an affected child is 1 in 4.

MSUD is diagnosed by biochemical analysis of urine organic acids by gas chromatography/mass spectrometry (GC/MS) and by assay of the BCKD enzyme activity. Patients with MSUD may have mutations in either the *BCKDHA* (19q13), *BCKDHB* (6p21), or *DBT* gene (1p31), which encode the E1 alpha, E1 beta, and DBT subunits of BCKD complex, respectively. Sequencing of BCKD complex genes is recommended after a biochemical diagnosis of BCKD deficiency and provides a complementary method to confirm the presence of mutations in a proband, identify carriers among the proband’s relatives, and prenatal diagnosis in families with known mutations.

Please [click here](#) for the GeneReviews summary on this condition.

### Genes

* **BCKDHA**, *BCKDHB*, *DBT*

### Indications

This test is indicated for:

- Individuals with biochemical diagnosis of MSUD.
- Family members of an individual with MSUD who are at risk to be carriers.

Sequencing is not appropriate for prenatal samples in which familial mutations have not been identified.

### Methodology

The 2-oxoisovaleratedehydrogenase alpha subunit (*BCKDHA*, E1 alpha) has 9 exons. The 2-oxoisovalerate dehydrogenase beta subunit (*BCKDHB*, E1 beta) and the lipoamide acyltransferase component (*DBT*, E2) each have 11 exons. The 31 coding exons and immediate flanking regions of the genes are amplified by PCR and sequenced in both forward and reverse directions. The patient's gene sequences are then compared to a normal reference sequence. Sequence variations are classified as previously described mutations, novel mutations, or variations of unknown significance. This analysis may detect novel variants of unclear effect which may require further studies.

**Targeted Array:**

DNA isolated from peripheral blood is hybridized to a CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes which cover the entire genomic region.

Please note that a “backbone” of probes across the entire genome are included on the array for analytical and quality control purposes. Rarely, off-target copy number variants causative of disease may be identified that may or may not be related to the patient’s phenotype. Only known pathogenic off-target copy number variants will be reported. Off-target copy number variants of unknown clinical significance will not be reported.

### Detection

Detection is limited to duplications and deletions. The CGH array will not detect point or intronic mutations.

Results of molecular analysis must be interpreted in the context of the patient’s clinical and/or biochemical phenotype.

### Specimen Requirements

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

**Type: Whole Blood**

Specimen Requirements:

- In EDTA (purple top) tube:
  - Infants (2 years): 3-5 ml
  - Older Children & Adults: 5-10 ml
Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Saliva**

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Special Instructions**

Please submit copies of diagnostic biochemical test results along with the sample. Contact the laboratory if further information is needed. Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of EGL Genetics, please submit a copy of the sequencing report with the test requisition.

**Related Tests**

- Organic Acid Analysis (OA) and Amino Acid Analysis (AA) - Plasma are used in the diagnoses of a patient with MSUD.
- BCKD Enzyme Activity Analysis (BC) is used to confirm the diagnosis of MSUD in a patient with elevations of branched chain amino acids.
- Known Mutation Analysis (KM) is available to family members if mutations are identified by sequencing.
- Prenatal testing is available to couples who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.