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| **Disease Name** | **Maple syrup urine disease** |
| **Alternate name(s)** | Branched chain ketoaciduria, Branched chain alpha-keto dehydrogenase deficiency |
| **Acronym** | MSUD type 1A, BCKD deficiency |
| **Disease Classification** | Amino Acid Disorder |
| **Variants** | Yes |
| **Variant name** | MSUD type 1B, MSUD Type II, Intermittent branched-chain ketoaciduria, Intermediate branched-chain ketoaciduria, Thiamine responsive MSUD |
| **Symptom onset** | Neonatal with some variability |
| **Symptoms** | Lethargy progressive to coma and possible death, vomiting, difficulty feeding, opisthotonic posturing, hypoglycemia, possible high pitched cry. |
| **Natural history without treatment** | Neurologic abnormalities and profound mental delays. |
| **Natural history with treatment** | Normal IQ and development may be expected if treatment is initiated before first crisis, but development is delayed in the severest cases. |
| **Treatment** | Dietary restriction of the branched chain amino acids and supplementation with medical formula. Thiamine supplementation in thiamine responsive patients. |
| **Other** | “Maple syrup”-like odor to urine (usually present during crisis) |
| **Physical phenotype** | None |
| **Inheritance** | Autosomal recessive |
| **General population incidence** | 1:200,000 |
| **Ethnic differences** | Yes |
| **Population** | Mennonites, French-Canadians |
| **Ethnic incidence** | 1/760 (Mennonites) |
| **Enzyme location** | Inner mitochondrial membrane; liver, kidney, leukocytes and fibroblasts. |
| **Enzyme Function** | Catalyzes the decarboxylation of oxoacids. |
| **Missing Enzyme** | Branched-chain ketoacid dehydrogenase (BCKAD). This enzyme is a multienzyme complex with 3 components – E1, E2 and E3. |
| **Metabolite changes** | Increased leucine, isoleucine and valine in plasma and urine, increased organic acids in urine. |
| **Prenatal testing** | Enzyme testing by CVS or amnio. If mutation is known, DNA testing may be available. |
| **MS/MS Profile** | Leucine elevated, leucine to alanine ratio elevated. |
| **OMIM Link** | http://www.ncbi.nlm.nih.gov/omim/248600 |
| **Genetests Link** | www.genetests.org |
| **Support Group** | The MSUD Family Support Group<br>http://www.msud-support.org<br>National Coalition for PKU and Allied Disorders<br>http://www.pku-allieddisorders.org/<br>Children Living with Inherited Metabolic Diseases<br>http://www.climb.org.uk/ |

# Newborn Screening ACT Sheet
# [Increased Leucine]
## Maple Syrup (Urine) Disease

**Differential Diagnosis:** Maple syrup urine disease (MSUD); hydroxyprolinemia (probably benign).

**Condition Description:** In MSUD, leucine, isoleucine, and valine (branched chain amino acids) cannot be metabolized further than their α-ketoacid derivatives. The amino acids and organic acids accumulate and produce severe toxicity.

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***YOU SHOULD TAKE THE FOLLOWING ACTIONS IMMEDIATELY:***

- Contact family to inform them of the newborn screening result and ascertain clinical status (poor feeding, vomiting, lethargy, tachypnea).
- Consult with pediatric metabolic specialist.
- Evaluate the newborn (poor feeding, lethargy, tachypnea, alternating hypertonia/hypotonia, seizures). If any sign is present or infant is ill, transport to hospital for further treatment in consultation with metabolic specialist.
- Initiate timely confirmatory/diagnostic testing and management, as recommended by specialist.
- Provide the family with basic information about MSUD and dietary management.
- Report findings to newborn screening program.

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**Diagnostic Evaluation:** In MSUD, plasma amino acid analysis reveals elevations of leucine, isoleucine, alloleucine, and valine (the branched chain amino acids); and urine organic acid analysis reveals abnormal branched-chain hydroxy- and ketoacids. In expanded screening, leucine/isoleucine and hydroxyproline cannot be differentiated, so if the baby has hydroxyprolinemia confirmatory amino acid analysis will show only increased hydroxyproline (a rare and likely benign entity).

**Clinical Considerations:** MSUD presents in the neonate with feeding intolerance, failure to thrive, vomiting, lethargy and maple syrup odor to urine and cerumen. If untreated, it will progress to irreversible mental retardation, hyperactivity, failure to thrive, seizures, coma, cerebral edema, and possibly death. Hydroxyprolinemia is probably benign.

**Additional Information:**

Emergency Protocols (New England Consortium of Metabolic Programs)
Gene Reviews
Genetics Home Reference

**Referral (local, state, regional and national):**

Testing
Clinical Services