

## **Metabolic Disorders**

## **Amino Acid Metabolism Disorders**

## Phenylketonuria (PKU)

Hyperphenylalanemia is an amino acid disorder caused by decreased activity, impaired synthesis or recycling of phenylalanine hydroxylase or its cofactor, BH<sub>4</sub>. Phenylketonuria (PKU) is caused by deficiency of phenylalanine hydroxylase. Without this enzyme, the body is unable to convert phenylalanine (PHE) into tyrosine (TYR). Phenylalanine accumulates in the blood, urine, and central nervous system.

If left untreated, the infant will experience profound **Intellectual disability** (ID). She or he could also have decreased pigmentation of the skin and hair, a musty odor, unusual behavior, and/or seizures. Screening for PKU can also identify infants with benign hyperphenylalaninemia, defects of biotin cofactor biosynthesis and defects of biotin cofactor regeneration.

Inheritance: Autosomal recessive

Estimated Incidence: PKU—1:16,000  
Benign hyperphenylalaninemia (H-PHE) - unknown  
Defects of biotin cofactors biosynthesis (BIOPT-BS) or  
regeneration (BIOPT-REG) —unknown, thought to be very rare

**Abnormal Screen Result: Elevated PHE  
Elevated PHE/TYR**

Method of Notification: All abnormal results are called to provider of record.

**Next Steps if Abnormal: Repeat amino acid profile** as soon as possible on filter paper. No formula/feeding change until results of repeat are known. If PHE is still elevated in the repeat specimen, **refer to a pediatric metabolic specialist.**

Further diagnostic evaluation may be necessary to rule out BH<sub>4</sub> defects. The metabolic specialist will initiate PHE restricted diet in coordination with a metabolic dietitian. **Report all findings to state newborn screening program.**

Neonatal Presentation: None.

Treatment: PKU/defects of biotin cofactor biosynthesis or regeneration: PHE restricted diet for life. Special metabolic formula is available to all SC residents, currently at no charge. BH<sub>4</sub> defects require additional diagnostic evaluation and treatment. Some persons with PKU are responsive to sapropterin, a pharmaceutical formulation of tetrahydrobiopterin, which can enhance residual phenylalanine hydroxylase activity.

Benign hyperphenylalaninemia: usually none

### **Special Considerations**

***Maternal PKU and Hyperphenylalaninemia***--Women with poorly controlled PKU have an increased risk of pregnancy loss. In studies of women with PKU, when PHE levels were not strictly controlled, the following outcomes were found in 90% of such pregnancies: intrauterine growth retardation, microcephaly, Intellectual disability (ID) and/or birth defects, particularly congenital heart defects.

Therefore, it is vital that women with PKU maintain phenylalanine levels between 120 and 360  $\mu\text{M/L}$ . Excellent control prior to conception and during pregnancy can help prevent damage to the developing fetus.

## Homocystinuria (HCY)

Homocystinuria (HCY) is caused primarily by a deficiency in the enzyme cystathionine synthetase leading to the accumulation of methionine (MET) in the blood. Untreated infants are at risk for Intellectual disability (ID), dislocated lens, marfanoid body type, developmental delay and thromboembolism.

Screening for homocystinuria may also identify infants with hypermethioninemia. Primary hypermethioninemia that is not caused by other disorders, liver disease or excess methionine intake appears to be extremely rare.

Inheritance: Autosomal recessive

Estimated Incidence: Homocystinuria—1:200,000  
Primary hypermethioninemia (HMET) - unknown, very rare

**Abnormal Screen Result:** **Elevated MET**  
**Elevated MET/PHE**

Method of Notification: All abnormal results are called to provider of record

**Next Steps if Abnormal:** **See infant as soon as possible** to ascertain health status and **repeat amino acid profile** on filter paper. **Consult pediatric metabolic specialist for further instructions.**

Initiate treatment and diagnostic evaluation as recommended by specialist. **Report all findings to state newborn screening program.**

Neonatal Presentation: None

Treatment: Some affected persons respond to Vitamin B6, the cofactor of cystathionine synthetase, with biochemical correction or improvement. If affected persons show only partial response or are nonresponsive to Vitamin B6, then a MET restricted diet for life is necessary. Betaine often used.

## Maple Syrup Urine Disease (MSUD)

Maple syrup urine disease (MSUD) is caused by deficiencies in the branched chain keto-acid dehydrogenase complex leading to the accumulation of leucine (LEU), isoleucine (ILE), valine (VAL) and alloisoleucine. Cerumen, urine or sweat may smell faintly of maple syrup.

Untreated infants with MSUD who survive infancy have retarded physical and mental development. Milder variants have been reported and may not be picked up by newborn screening.

Inheritance: Autosomal recessive

Estimated Incidence: 1:185,000

**Abnormal Screen Result:** Elevated LEU+ILE  
Elevated VAL  
Elevated LEU+ILE/PHE  
Elevated VAL/PHE

Method of Notification: All abnormal results are called to provider of record

**Next Steps if Abnormal:** Potential medical emergency! See infant as soon as possible to ascertain health status and repeat amino acid profile on filter paper. Consult pediatric metabolic specialist for further instructions.

Initiate treatment and diagnostic evaluation as recommended by specialist. **Report all findings to state newborn screening program.**

Neonatal Presentation: May show neurological impairment in first week of life. Lethargy and poor suck are often the first signs followed by abnormal muscle tone, involuntary movements, seizures and coma.

Treatment: LEU restricted/ILE, VAL controlled diet for life. Some affected persons with a less severe form of MSUD are thiamin responsive.

### Special Considerations

**Fastening/infection/intercurrent illness** - Parents must clearly understand that minor illnesses can precipitate metabolic decompensation in an infant/child with this disorder and should seek medical attention with any concern. Urinary ketones may be monitored as a precaution during illness. Ketonuria can be an early sign of metabolic decompensation and frequently precedes clinical signs.

## Citrullinemia

Citrullinemia I (CIT I) is a urea cycle disorder caused primarily by a deficiency of the enzyme Argininosuccinic acid synthetase. Citrulline (CIT) and ammonia build up in the blood which can lead to lethargy, seizures, coma and death. Citrullinemia II (CIT II) is also a urea cycle disorder. It is caused by a deficiency of the protein citrin which is necessary for many metabolic processes. In the neonatal onset type of CIT II, bile flow is blocked.

Inheritance: Autosomal recessive

Estimated Incidence: CIT I—1:57,000  
CIT II—1:100,000 primarily in persons of Japanese, East Asian or Middle Eastern ancestry

**Abnormal Screen Result:** Elevated CIT

Method of Notification: All abnormal results are called to provider of record

**Next Steps if Abnormal:** **Potential medical emergency! See infant as soon as possible to ascertain health status. Consult pediatric metabolic specialist for further instructions. Emergency treatment may include provision of sufficient nonprotein calories to prevent catabolism; Na benzoate or Na phenylacetate; IV arginine.**

**Dialysis may be necessary to lower ammonia level.**

**Repeat amino acid profile** as soon as possible on filter paper. Initiate treatment and diagnostic evaluation as recommended by specialist. **Report all findings to state newborn screening program.**

Neonatal Presentation: May show neurological deterioration in first week of life. Lethargy, poor feeding, vomiting, grunting respirations, tachypnea, and hypothermia progress to seizures, encephalopathy and death unless quickly treated.

Treatment: High calorie, protein restricted, ARG supplemented diet. Na benzoate, Na phenylacetate, Na phenylbutyrate may be used to help decrease accumulated toxic precursors

### **Special Considerations**

***Fasting/infection/intercurrent illness*** - Parents must clearly understand that minor illness can precipitate metabolic decompensation in an infant/child with this disorder and should seek medical attention with any concern.

## Argininosuccinic Aciduria (ASA)

Argininosuccinic aciduria (ASA) is a urea cycle disorder caused primarily by a deficiency of the enzyme Argininosuccinic acid lyase. Argininosuccinic acid, citrulline (CIT) and ammonia build up in the blood which can lead to lethargy, seizures, coma and death.

Inheritance: Autosomal recessive

Estimated Incidence: 1:70,000

**Abnormal Screen Result: Elevated CIT**

Method of Notification: All abnormal results are called to provider of record

**Next Steps if Abnormal: Potential medical emergency! See infant as soon as possible to ascertain health status. Consult pediatric metabolic specialist for further instructions. Emergency treatment may include provision of sufficient nonprotein calories to prevent catabolism, Na benzoate or Na phenylacetate, IV arginine.**

**Dialysis may be necessary to lower ammonia level.**

**Repeat amino acid profile** as soon as possible on filter paper. Initiate treatment and diagnostic evaluation as recommended by specialist. **Report all findings to state newborn screening program.**

Neonatal Presentation: May show neurological deterioration in first week of life. Lethargy, poor feeding, vomiting, respiratory alkalosis, and hypothermia progress to seizures, encephalopathy and death unless quickly treated.

Treatment: High calorie, protein restricted, ARG supplemented diet. Na benzoate, Na phenylacetate, Na phenylbutyrate may be used to help decrease accumulated toxic precursors.

### Special Considerations

**Fasting/infection/intercurrent illness** - Parents must clearly understand that minor illness can precipitate metabolic decompensation in an infant/child with this disorder and should seek medical attention with any concern.

## Tyrosinemia

Tyrosinemia I (TYR I) is caused by a deficiency in the enzyme fumarylacetoacetase. Untreated infants are at risk for liver failure, jaundice, growth retardation and eventual hepatocellular carcinoma. Tyrosinemia Type II or III (TYR II or III) can also be identified by screening. TYR II is caused by a deficiency in the enzyme tyrosine aminotransferase. TYR III is caused by a deficiency in the enzyme 4-OH phenylpyruvate dioxygenase.

Untreated infants with TYR II are at risk for eye and skin lesions with neurological problems including developmental delay. The clinical features of TYR III are not well described. However, Intellectual disability (ID) and behavioral problems have been found in affected persons.

Inheritance: Autosomal recessive

Estimated Incidence: TYR I - 1:100,000  
TYR II - 1:250,000  
TYR III - unknown, thought to be very rare

**Abnormal Screen Result:** TYR I - Elevated TYR and succinyl acetone (SUAC)  
TYR II or III - Elevated TYR with normal SUAC

Method of Notification: All abnormal SUAC results are called to provider of record. TYR results greater than 800  $\mu\text{M}$  are called to the provider of record. Other abnormal TYR results are mailed to provider of record.

**Next Steps if Abnormal:** See infant as soon as possible to ascertain health status and repeat SUAC and amino acid profile on filter paper. Consult pediatric metabolic specialist for further instructions.

Initiate treatment and diagnostic evaluation as recommended by specialist. **Report all findings to state newborn screening program.**

Neonatal Presentation: All forms—usually none.

Treatment: TYR I: TYR and PHE restricted diet for life. NTBC (Nitisinone) also used to inhibit the degradation of tyrosine and the formation of toxic metabolites. Liver transplantation, if indicated.

TYR II or III: TYR and PHE restricted diet for life.

### Special Considerations

**Premature/sick infants** - Transient Tyrosinemia of the Newborn is the most common amino acid disorder found in infants, especially those who are premature and/or sick. However, prompt repeat screening is needed as a precaution.

## **Carbohydrate Metabolism Disorders**

## Galactosemia

Galactosemia is a condition of abnormal galactose metabolism caused by deficient functioning of any of three separate enzymes. These include galactose-1-P-uridyl transferase (**GALT**) deficiency or classic galactosemia; galactokinase deficiency (**GALK**); and UDP galactose-4-epimerase deficiency (**GALE**). Individuals with galactosemia are unable to break down and use the sugar galactose (a component of lactose found primarily in dairy products and human milk).

If undiagnosed, the affected infant with classical galactosemia may develop gastrointestinal disturbances, fail to gain weight and become jaundiced. Life-threatening infection can occur in the newborn period. Intellectual disability (ID) and delayed physical growth occur in untreated infants who survive.

Some infants with low levels of GALT are subsequently diagnosed with a form of galactosemia called Duarte variant galactosemia. Almost all cases of Duarte variant galactosemia are benign; however, a few affected infants may be treated during the first year of life as a precaution.

Infants with GALK deficiency only have cataracts. Infants with GALE deficiency will have varying outcomes. If the GALE deficiency is localized in the red blood cell, the infant does not have any symptoms of disease and no treatment is necessary. If the GALE deficiency involves other tissues, the clinical course is like that of GALT deficiency. The diagnostic work-up may also identify infants who are genetic carriers for one of the forms of galactosemia.

Inheritance: Autosomal recessive

Estimated Incidence: GALT (classic galactosemia)—1:60,000  
Duarte variant galactosemia—1:16,000  
GALK unknown, thought to be rare  
GALE unknown, thought to be very rare

**Abnormal Screen Result: Elevated total galactose with low GALT: at risk for classical galactosemia.**

**Normal total galactose with very low GALT: at risk for Duarte galactosemia, or at risk for classical galactosemia, if infant on non-lactose feeding at time of screening.**

**Elevated total galactose with normal GALT: at risk for GALK or GALE deficiency.**

Method of Notification: All results where the GALT is low and total galactose is elevated are called to provider of record. Other combinations of results are mailed to provider of record.

**Next Steps if Abnormal: Potential medical emergency when GALT is low and total galactose is elevated. See infant as soon as possible to ascertain**

health status. Change to soy based formula when GALT is low and total galactose is elevated. **Report all findings to state newborn screening program.**

If total galactose is not elevated, consider change to soy based formula based upon clinical observation and recommendation from pediatric metabolic specialist. In most circumstances, at least partial breastfeeding is possible if total galactose is not elevated.

Repeat galactosemia screening as soon as possible. Consult pediatric metabolic specialist for further instructions and diagnostic evaluation.

**If GALT is normal in the initial specimen, repeat galactosemia screening as soon as possible. NO NEED TO STOP BREAST FEEDING OR CHANGE FORMULA TYPE at this time.**

If total galactose remains elevated in the repeat specimen or if the GALT result is now low, consult pediatric metabolic specialist for further diagnostic evaluation and feeding recommendations.

Neonatal Presentation: GALT - hypoglycemia, jaundice, sepsis, failure to thrive  
Duarte variant galactosemia - None  
GALK - None  
GALE - Usually none

Treatment: Galactose restricted diet for life.

### **Special Considerations**

***Reporting of Feeding Type*** - It is crucial that staff report whether the infant is on a lactose containing feeding (breast milk or cow's milk based infant formula), a soy based infant formula or any other non-lactose containing feeding (including IV fluids or total parenteral nutrition/hyperalimentation) so that the lab test can be interpreted appropriately.

***Exposure of the Specimen to Heat/Humidity*** - Both heat and humidity can affect the test for GALT. The enzyme activity can be diminished causing a false positive result for galactosemia.

***Transfusion*** - Transfusion of red blood cells prior to drawing the newborn screening specimen may affect the GALT result. Repeat screening for galactosemia should be done 120 days after the last transfusion. If the date of the last transfusion is unknown, put the date of hospital discharge on the collection form.

# **Organic Acid Metabolism Disorders**

## Propionic Acidemia (PROP)

Propionic acidemia is a disorder of isoleucine (ILE), methionine (MET), threonine (THR), valine (VAL), and odd chain fatty acid metabolism caused by deficient activity of the enzyme propionyl coenzyme A carboxylase. This enzyme deficiency leads to the accumulation of toxic organic acid metabolites when the affected infant is ingesting a normal diet or is under catabolic stress.

Inheritance: Autosomal recessive

Estimated Incidence: 1:100,000

**Abnormal Screen Result: Elevated C3 (propionyl carnitine)  
Elevated C3/C2  
Elevated C3/C16**

Method of Notification: All results where the C3 is greater than 10  $\mu\text{M}$  and the C3/C2 and/or C3/C16 is elevated are called to provider of record. All results where the C3 is greater than 15  $\mu\text{M}$  are called to the provider of record, regardless of the ratio levels. Any other abnormal C3 results are mailed to the provider of record.

**Next Steps if Abnormal: Potential medical emergency when the C3 is greater than 10  $\mu\text{M}$  and the C3/C2 and/or C3/C16 is elevated or when the C3 is greater than 15  $\mu\text{M}$ , regardless of the ratio levels. See infant as soon as possible to ascertain health status. Consult pediatric metabolic specialist for further instructions.**

**Repeat acyl carnitine profile** as soon as possible on filter paper. Initiate treatment and diagnostic evaluation as recommended by specialist. **Report all findings to state newborn screening program.**

Neonatal Presentation: Poor feeding, vomiting, tachypnea, lethargy, abnormal muscle tone, involuntary movements, seizures, coma

Treatment: Protein restricted diet. Use of metabolic formula without ILE, MET, THR, VAL. Carnitine supplementation. Biotin trial.

### Special Considerations

***Fasting/infection/intercurrent illness*** - Parents must clearly understand that minor illnesses can precipitate metabolic decompensation in an infant/child with an organic acid disorder and should seek medical attention with any concern. Urinary ketones may be monitored as a precaution during illness. Ketonuria can be an early sign of metabolic decompensation and frequently precedes clinical signs.

## Malonic Acidemia (MAL)

Malonic acidemia is a disorder of ketone metabolism arising from a deficiency of the enzyme malonyl CoA decarboxylase. Almost all affected infants have developmental delay. Other findings include hypotonia, seizures, hypoglycemia and cardiomyopathy. To date, fewer than 30 cases of malonic acidemia have been reported.

Inheritance: Autosomal recessive

Estimated Incidence: Unknown; thought to be very rare

**Abnormal Screen Result:** **Elevated C3DC (malonyl carnitine) + C4OH (3-OH butyryl carnitine)**

**Elevated C3DC (malonyl carnitine) + C4OH (3-OH butyryl carnitine)/C10 (decanoyl carnitine) ratio**

Method of Notification: All results where the C3DC + C4OH/C10 is greater than 5 are called to provider of record.

**Next Steps if Abnormal:** **See infant as soon as possible** to ascertain health status and **repeat acyl carnitine profile** on filter paper. **Consult pediatric metabolic specialist for further instructions.**

Initiate treatment and diagnostic evaluation as recommended by specialist. **Report all findings to state newborn screening program.**

Neonatal Presentation: May have hypotonia, hypoglycemia, hypertrophic cardiomyopathy, diarrhea, vomiting, ketosis and/or seizures. Infants are at risk for metabolic decompensation/crisis.

Treatment: Carnitine supplementation. May be prescribed fat controlled diet with MCT as major fat source. Avoid fasting.

## Methylmalonic Acidemia (MUT & Cbl A, B)

Methylmalonic academia is a disorder of isoleucine (ILE), methionine (MET), threonine (THR), valine (VAL), and odd chain fatty acid metabolism caused by deficient methyl malonyl CoA mutase, deficient Vitamin B12 (cobalamin) or defects in absorption, transport or processing of cobalamin. Toxic organic acid metabolites accumulate when the affected infant is ingesting a normal diet or is under catabolic stress.

Inheritance: Autosomal recessive

Estimated Incidence: Vitamin B 12 non-responsive 1:48,000  
1 out of every 50,000 to 100,000

**Abnormal Screen Result: Elevated C3 (propionyl carnitine)  
Elevated C3/C2  
Elevated C3/C16**

Method of Notification: All results where the C3 is greater than 10  $\mu\text{M}$  and the C3/C2 and/or C3/C16 is elevated are called to provider of record. All results where the C3 is greater than 15  $\mu\text{M}$  are called to the provider of record, regardless of the ratio levels. Any other abnormal C3 results are mailed to the provider of record.

**Next Steps if Abnormal: Potential medical emergency when the C3 is greater than 10  $\mu\text{M}$  and the C3/C2 and/or C3/C16 is elevated or when the C3 is greater than 15  $\mu\text{M}$  regardless of the ratio levels. See infant as soon as possible to ascertain health status. Consult pediatric metabolic specialist for further instructions.**

**Repeat acyl carnitine profile** as soon as possible on filter paper. Initiate treatment and diagnostic evaluation as recommended by specialist. **Report all findings to state newborn screening program.**

Neonatal Presentation: Poor feeding, vomiting, tachypnea, lethargy, abnormal muscle tone, involuntary movements, seizures, coma

Treatment: Trial of hydroxy cobalamin as soon as suspected. Protein restricted diet. Use of metabolic formula without ILE, MET, THR, VAL. Carnitine supplementation.

### Special Considerations

***Fasting/infection/intercurrent illness***—Parents must clearly understand that minor illnesses can precipitate metabolic decompensation in an infant/child with an organic acid disorder and should seek medical attention with any concern. Urinary ketones may be monitored as a precaution during illness. Ketonuria can be an early sign of metabolic decompensation and frequently precedes clinical signs.

## **Methylmalonic Acidemia with Homocystinuria (CBL C, D, F)**

Methylmalonic acidemia is an inherited condition in which the body is unable to process certain fats and proteins. It is considered an organic acid condition because it can lead to a harmful excess of certain toxins and organic acids.

Methylmalonic acidemia with homocystinuria (Cbl C, D, F) is one rare type of methylmalonic acidemia. Individuals with this form of methylmalonic acidemia have trouble producing certain cobalamin enzymes, which causes harmful levels of homocysteine and methylmalonic acid to build up in their bodies.

**Abnormal Screen Result:**    **Elevated C3 (propionyl carnitine)**  
   **Decreased MET (Methionine)**  
   **Elevated C3/C2**

The exact number of people affected by this specific disorder is currently unknown. Signs of methylmalonic acidemia with homocystinuria (Cbl C, D, F) could begin anywhere between the first few days of life and 14 years of age. Children with Cbl C usually show symptoms between the first few days and the first month of life. Children with Cbl D deficiency do not show signs until later in childhood.

Infants with Cbl C, D, or F, may exhibit signs including delayed growth, small head size, skin rash, vomiting, poor appetite, diarrhea, fever, sleeping longer or more often, tiredness or weak muscle tone (called hypotonia).

Many of these signs may occur when your baby eats foods that their body cannot break down. They can be triggered by long periods of time without eating, illnesses, and infections.

### **Dietary Treatment:**

A restricted diet to avoid proteins that the body cannot break down. Special formulas or foods may be recommended; these formulas will likely need to continue through adulthood.

Eating often will also help prevent many of the signs mentioned above. Illnesses and infections can also trigger these signs.

### **Supplements and Medications:**

Natural supplements can also help treat Cbl C, D, F. Vitamin B-12 can help reduce the signs and symptoms of the condition in some children.

## Isobutyryl Glycinuria (IBG)

Iso-Butyryl-Glycinuria is a disorder of valine metabolism. Infants with this disorder may have cardiomyopathy and anemia.

Inheritance:	Presumed autosomal recessive
Estimated Incidence:	Unknown; thought to be very rare
<b>Abnormal Screen Result:</b>	<b>Elevated C4 (butyryl carnitine)</b>
Method of Notification:	All abnormal results are called to provider of record
<b>Next Steps if Abnormal:</b>	<b>See infant as soon as possible</b> to ascertain health status and <b>repeat acyl carnitine profile</b> on filter paper. <b>Consult pediatric metabolic specialist for further instructions.</b>  Initiate treatment and diagnostic evaluation as recommended by specialist. <b>Report all findings to state newborn screening program.</b>
Neonatal Presentation:	None
Treatment:	Carnitine supplementation. Moderate protein restriction and avoidance of fasting may be helpful.

## Isovaleric Acidemia (IVA)

Isovaleric acidemia is a disorder of leucine (LEU) metabolism caused by deficiency of the enzyme isovaleryl CoA dehydrogenase. This enzyme deficiency leads to the accumulation of toxic organic acid metabolites when the affected infant is ingesting a normal diet or is under catabolic stress. A chronic, intermittent form of IVA can present later in infancy or childhood with episodes of metabolic acidosis, usually associated with an intercurrent illness or increased protein intake.

Inheritance: Autosomal recessive

Estimated Incidence: 1:230,000

**Abnormal Screen Result: Elevated C5 (isovaleryl carnitine)**

Method of Notification: All abnormal results are called to provider of record

**Next Steps if Abnormal: Potential medical emergency! See infant as soon as possible to ascertain health status and repeat acyl carnitine profile on filter paper. Consult pediatric metabolic specialist for further instructions.**

**Initiate treatment and diagnostic evaluation as recommended by specialist. Report all findings to state newborn screening program.**

Neonatal Presentation: Poor feeding, vomiting, tachypnea, lethargy, abnormal muscle tone, involuntary movements, seizures, coma

Treatment: Protein restricted diet. Use of metabolic formula without LEU. Glycine (GLY) supplementation. Carnitine supplementation.

### **Special Considerations**

***Fasting/infection/intercurrent illness*** - Parents must clearly understand that minor illnesses can precipitate metabolic decompensation in an infant/child with an organic acid disorder and should seek medical attention with any concern. Urinary ketones may be monitored as a precaution during illness. Ketonuria can be an early sign of metabolic decompensation and frequently precedes clinical signs.

## 2-Methylbutyrylglycinuria (2MBG)

2-Methylbutyryl CoA dehydrogenase deficiency is a disorder of isoleucine (ILE) metabolism. Infants with this disorder may be asymptomatic or may have an episode of metabolic decompensation with subsequent neurological deficits.

Inheritance: Presumed autosomal recessive

Estimated Incidence: Unknown; thought to be very rare outside of persons of Hmong ancestry

**Abnormal Screen Result: Elevated C5 (isovaleryl carnitine)**

Method of Notification: All abnormal results are called to provider of record

**Next Steps if Abnormal: See infant as soon as possible to ascertain health status and repeat acyl carnitine profile on filter paper. Consult pediatric metabolic specialist for further instructions.**

Initiate treatment and diagnostic evaluation as recommended by specialist. **Report all findings to state newborn screening program.**

Neonatal Presentation: Hypotonia, lethargy, apnea, hypoglycemia

Treatment: Carnitine supplementation. Moderate protein restriction. Avoid fasting.

### 3-Methylcrotonyl CoA Carboxylase Deficiency (3-MCC)

3-Methylcrotonyl CoA carboxylase deficiency (3-MCC) is a disorder of leucine (LEU) metabolism. Infants may have a Reye-like illness with hypoketotic hypoglycemia, hypotonia, hepatic encephalopathy, and metabolic acidosis. Symptomatic infants may have a “cat’s urine” odor.

Inheritance: Autosomal recessive

Estimated Incidence: 1:50,000

**Abnormal Screen Result:** Elevated C4DC (methyl malonyl carnitine) + C5OH (3-OH isovaleryl carnitine)

Method of Notification: All abnormal results are called to provider of record

**Next Steps if Abnormal:** See infant as soon as possible to ascertain health status and repeat acyl carnitine profile on filter paper. Consult pediatric metabolic specialist for further instructions.

Initiate treatment and diagnostic evaluation as recommended by specialist. Report all findings to state newborn screening program.

Neonatal Presentation: Usually none. May present with seizures.

Treatment: Carnitine supplementation. Moderate protein and LEU restriction. Glycine supplementation. Avoid fasting. NOTE: Biotin is **not** effective in isolated 3-MCC.

#### Special Considerations:

**Maternal 3-MCC:** In some newborns, the elevated C4DC+C5OH is reflective of maternal 3-MCC levels.

## Beta Ketothiolase Deficiency

Beta Ketothiolase Deficiency ( $\beta$ KT) is a disorder of isoleucine (ILE) metabolism and of ketolysis. Infants with this disorder are at risk for episodes of severe ketoacidosis with subsequent neurological deficits. This disorder is sometimes called 2-methyl 3-OH butyric aciduria.

Inheritance: Autosomal recessive

Estimated Incidence: Unknown

**Abnormal Screen Result:** **Elevated C4DC (methyl malonyl carnitine) + C5OH (3-OH isovaleryl carnitine)**

Method of Notification: All abnormal results are called to provider of record

**Next Steps if Abnormal:** **See infant as soon as possible** to ascertain health status and **repeat acyl carnitine profile** on filter paper. **Consult pediatric metabolic specialist for further instructions.**

Initiate treatment and diagnostic evaluation as recommended by specialist. **Report all findings to state newborn screening program.**

Neonatal Presentation: Poor feeding, vomiting, tachypnea, lethargy

Treatment: Carnitine supplementation. Protein restricted/fat controlled diet. Avoid fasting. May require long term bicarbonate.

### Special Considerations

**Fasting/infection/intercurrent illness** - Parents must clearly understand that minor illnesses can precipitate metabolic decompensation in an infant/child with an organic acid disorder and should seek medical attention with any concern.

Urinary ketones should be monitored at home. Ketonuria can be an early sign of metabolic decompensation and frequently precedes clinical signs.

## 2-Methyl 3-OH Butyric Aciduria (2M3HBA)

2-methyl 3-OH butyric aciduria is a disorder of isoleucine (ILE) metabolism and of 2-methyl branched chain fatty acids. Infants with this disorder are at risk for episodes of metabolic decompensation, usually after a stressor. Reported cases have shown progressive loss of motor skills, choreoathetosis, dystonia and seizures.

Inheritance: Thought to be X-linked, but an affected female has been identified.

Estimated Incidence: Unknown; thought to be very rare

**Abnormal Screen Result:** **Elevated C4DC (methyl malonyl carnitine) + C5OH (3-OH isovaleryl carnitine)**  
**Elevated C5:1 (tiglyl carnitine)**

Method of Notification: All abnormal results are called to provider of record

**Next Steps if Abnormal:** **See infant as soon as possible** to ascertain health status and **repeat acyl carnitine profile** on filter paper.

**Consult pediatric metabolic specialist for further instructions.**  
Initiate treatment and diagnostic evaluation as recommended by specialist. **Report all findings to state newborn screening program.**

Neonatal Presentation: Usually none

Treatment: ILE and protein restricted diet

## HMG-CoA lyase deficiency (HMG)

HMG-CoA lyase deficiency (also known as 3-hydroxy-3-methylglutaric aciduria) is a disorder of leucine (LEU) metabolism and of ketogenesis. Infants with this disorder may present with hypoketotic hypoglycemia and are at risk for subsequent neurological deficits.

Inheritance: Autosomal recessive

Estimated Incidence: Unknown, thought to be rare

**Abnormal Screen Result:** Elevated C4DC (methyl malonyl carnitine) + C5OH (3-OH isovaleryl carnitine)

Method of Notification: All abnormal results are called to provider of record

**Next Steps if Abnormal:** See infant as soon as possible to ascertain health status and repeat acyl carnitine profile on filter paper. Consult pediatric metabolic specialist for further instructions.

Initiate treatment and diagnostic evaluation as recommended by specialist. **Report all findings to state newborn screening program.**

Neonatal Presentation: One-third of affected newborns will have hypoketotic hypoglycemia, severe metabolic acidosis, vomiting, lethargy, hypotonia

Treatment: Protein restricted diet. Use of metabolic formula without LEU. Carnitine supplementation. Fat controlled diet when older. Avoid fasting.

### Special Considerations

**Fasting/illness/protein loading** - Parents must clearly understand that minor illness can precipitate metabolic decompensation in an infant/child with this disorder and should seek medical attention with any concern.

Protein loading or fasting can also lead to hypoglycemic episodes resulting in seizures or coma.

### 3-Methylglutaconic Aciduria (3MGA)

3-Methylglutaconic Aciduria is a disorder of leucine (LEU) metabolism. Three other types of 3-methylglutaconic aciduria have also been described.

Mildly affected persons have speech retardation and short attention span. Severely affected persons have had acidosis and more severe neurological problems, hypotonia, spastic dystonia, irritability, developmental delay and Intellectual disability (ID).

Inheritance:	Autosomal recessive
Estimated Incidence:	Unknown, thought to be very rare
<b>Abnormal Screen Result:</b>	<b>Elevated C4DC (methyl malonyl carnitine) + C5OH (3-OH isovaleryl carnitine)</b>
Method of Notification:	All abnormal results are called to provider of record
<b>Next Steps if Abnormal:</b>	<b>See infant as soon as possible</b> to ascertain health status and <b>repeat acyl carnitine profile</b> on filter paper. <b>Consult pediatric metabolic specialist for further instructions.</b>  Initiate treatment and diagnostic evaluation as recommended by specialist. <b>Report all findings to state newborn screening program.</b>
Neonatal Presentation:	None reported
Treatment:	Carnitine supplementation. Moderate protein and LEU restriction. Avoid fasting.

## Multiple Carboxylase Deficiency (MCD) aka Holocarboxylase Synthetase Deficiency

Multiple carboxylase deficiency is caused by a deficiency of the enzyme holocarboxylase synthetase. This enzyme activates four carboxylases by attaching biotin. These carboxylases are involved in amino acid metabolism, gluconeogenesis, and fatty acid synthesis. Affected infants may develop severe metabolic acidosis leading to coma. Skin rash and hair loss occur at later stages.

Inheritance: Autosomal recessive

Estimated Incidence: 1:87,000

**Abnormal Screen Result:** Elevated C3 (propionyl carnitine)  
Elevated C4DC (methyl malonyl carnitine) + C5OH (3-OH isovaleryl carnitine)

Method of Notification: All results where both C3 and C4DC+C5OH are elevated are called to the provider of record.

**Next Steps if Abnormal:** See infant as soon as possible to ascertain health status and repeat acyl carnitine profile on filter paper. Consult pediatric metabolic specialist for further instructions.

Initiate treatment and diagnostic evaluation as recommended by specialist. **Report findings to state newborn screening program.**

Neonatal Presentation: May show food refusal, vomiting, lethargy, seizures, hypotonia, tachypnea

Treatment: Biotin supplementation

### Special Considerations

**Enzymes necessary for carboxylase activity** - Two enzymes are necessary for normal activity of four carboxylases: holocarboxylase synthetase to attach biotin to the carboxylases and biotinidase to free the protein bound biotin.

## Glutaric Aciduria Type I (GA I)

Glutaric aciduria type I is caused by a deficiency in the enzyme glutaryl CoA dehydrogenase. Seventy percent of infants will have macrocephaly at or shortly after birth. Infants may remain asymptomatic until an encephalopathic crisis. Others gradually develop motor delay and hypotonia without any apparent acute crisis. No loss of intellectual capacity develops unless a neurological crisis occurs.

Inheritance: Autosomal recessive

Estimated Incidence: 1:40,000

**Abnormal Screen Result:** Elevated C5DC (glutaryl carnitine) + C6OH (3-OH hexanoyl carnitine)

Method of Notification: All abnormal results as determined by the R4S/CLIR Post Analytical Tool are called to provider of record.

**Next Steps if Abnormal:** **Potential medical emergency! See infant as soon as possible to ascertain health status. Consult pediatric metabolic specialist for further instructions. A portion of the initial specimen will be sent to the Greenwood Genetic Center Laboratory for secondary testing.**

**Repeat acyl carnitine profile** as soon as possible on filter paper. Collection of other specimens may be indicated depending upon the results of secondary testing.

Initiate treatment and diagnostic evaluation as recommended by specialist. **Report all findings to state newborn screening program.**

Neonatal Presentation: Macrocephaly, irritability, jitteriness, hypotonia

Treatment: Prompt treatment of catabolic events. Aggressive fever control. Watch fluid intake, as affected persons may have profuse sweating. Riboflavin trial. Carnitine supplementation. Protein restricted diet. Use of metabolic formula without lysine (LYS) and tryptophan (TRP).

### Special Considerations

**Fasting/infection/intercurrent illness** - Parents must clearly understand that minor illnesses can precipitate encephalopathic or metabolic decompensation in an infant/child with this disorder. Hospital admission may be considered mandatory for IV fluids with any vomiting illness.

***Fever*** - Poorly controlled/untreated persons with GA I may have recurrent fever not related to illness. Death from hyperthermia has been reported in children with GA I.

***Acute subdural and/or retinal hemorrhages***—Infants with GA I are prone to acute subdural and/or retinal hemorrhage after minor head trauma (i.e., minor childhood falls that can occur when infant is learning to walk) that can be misdiagnosed as child abuse.

## **Fatty Acid Oxidation Disorders**

## Medium Chain Acyl Co-A Dehydrogenase Deficiency (MCAD)

Medium chain acyl Co-A dehydrogenase deficiency (MCAD) is an inborn error of fatty acid oxidation that can cause significant morbidity and mortality in the newborn. It usually presents in infancy or early childhood with hypoketotic hypoglycemia and encephalopathy after an intercurrent illness and/or period of poor oral intake.

Approximately 20% of infants with MCAD die before diagnosis, and a substantial proportion of the survivors have significant residual problems from an initial crisis. Children who survive the initial crises may have developmental delay, seizures, speech/language delays, chronic muscle weakness, failure to thrive, cerebral palsy and attention deficit disorder.

Inheritance: Autosomal recessive

Estimated Incidence: 1:16,000

**Abnormal Screen Result: Primary Markers**  
**Elevated C8 (octanoyl carnitine)**  
**Elevated C10 (decanoyl carnitine)**  
**Elevated C10:1 (decenoyl carnitine)**

**Secondary Markers**  
**Elevated C6 (hexanoyl carnitine)**  
**Elevated C8/C10**

Method of Notification: All abnormal results where the C8 is elevated are called to provider of record. Isolated elevations of secondary markers have no clinical significance and are not reported.

**Next Steps if Abnormal: See infant as soon as possible to ascertain health status and repeat acyl carnitine profile on filter paper. Consult pediatric metabolic specialist for further instructions.**

Initiate treatment and diagnostic evaluation as recommended by specialist. **Report all findings to state newborn screening program.**

Neonatal Presentation: Usually none

Treatment: Avoid fasting. Supplementation with high energy carbohydrate drinks during periods of illness. Seek medical attention if these liquids are refused. Oral rehydration fluids are not adequate. If oral feedings are not possible, then intravenous fluids with concentrated dextrose should be started without waiting for symptoms of decompensation to develop.

Infants with MCAD must be fed at least every three to four hours, including at night.

**Infants with MCAD should not be fed formulas that have medium chain triglycerides (MCT) as the primary fat source if a safe alternative is available.** Feeding intervals can be lengthened as the infant gets older.

Carnitine supplementation if helpful.

### **Special Considerations**

***Fasting/infection/intercurrent illness*** - Parents must clearly understand that prolonged fasting and infection/intercurrent illnesses can cause serious complications in an infant with MCAD. These outcomes include hypoketotic hypoglycemia, vomiting, lethargy, seizures and coma.

Infants experiencing stressful events such as trauma, infections/illnesses, and even receiving immunizations should be monitored to prevent hypoglycemic episodes. Blood glucose may be monitored as a precaution.

***Premature/sick infants*** - Some special formulas and breast milk fortifiers fed to premature/sick infants contain medium chain triglycerides (MCT) as the primary fat source. These feedings may cause false elevations of some acyl carnitines analyzed in MCAD screening, particularly C8, C10:1 and C8/C10.

## Medium Chain Ketoacyl CoA Thiolase Deficiency (MCAT)

Medium chain ketoacyl CoA Thiolase deficiency (MCAT) is an inborn error of fatty acid oxidation. Only one infant with this disorder has been detected worldwide. This male neonate presented with vomiting, dehydration, metabolic acidosis, liver dysfunction, and terminal rhabdomyolysis with myoglobinuria.

Inheritance: Unknown

Estimated Incidence: Extremely rare

**Abnormal Screen Result: Elevated C8 (octanoyl carnitine)**

Method of Notification: All abnormal results are called to provider of record

**Next Steps if Abnormal: See infant as soon as possible to ascertain health status and repeat acyl carnitine profile on filter paper. Consult pediatric metabolic specialist for further instructions.**

Initiate treatment and diagnostic evaluation as recommended by specialist. **Report all findings to state newborn screening program.**

Neonatal Presentation: Vomiting, dehydration, metabolic acidosis, liver dysfunction

Treatment: Only known affected infant died at 13 days of life. Presumed treatment is same as that for other fatty acid metabolism disorders: Avoid fasting. Supplementation with high energy carbohydrate drinks during periods of illness.

Seek medical attention if these liquids are refused. Oral rehydration fluids are not adequate. If oral feedings are not possible, then intravenous fluids with concentrated dextrose should be started without waiting for symptoms of decompensation to develop.

Feed at least every three to four hours, including at night.

### Special Considerations

**Fasting/infection/intercurrent illness** - Parents must clearly understand that prolonged fasting and infection/intercurrent illnesses can cause serious complications in an infant with a fatty acid oxidation disorder. Infants experiencing stressful events such as trauma, infections/illnesses, and even receiving immunizations should be monitored to prevent metabolic decompensation.

## Short Chain Acyl Co-A Dehydrogenase Deficiency (SCAD)

Short chain acyl Co-A dehydrogenase deficiency (SCAD) is an inborn error of fatty acid oxidation. Outcome in affected persons have been quite variable. Infants may have seizures, poor feeding, progressive muscle weakness, developmental delay and hypotonia.

Inheritance: Autosomal recessive

Estimated Incidence: 1:40,000 to 1:100,000

**Abnormal Screen Result: Elevated C4 (butyryl carnitine)**

Method of Notification: All abnormal results are called to provider of record

**Next Steps if Abnormal: See infant as soon as possible to ascertain health status and repeat acyl carnitine profile on filter paper. Consult pediatric metabolic specialist for further instructions.**

Initiate treatment and diagnostic evaluation as recommended by specialist. **Report all findings to state newborn screening program.**

Neonatal Presentation: Poor feeding, vomiting, lethargy, seizures, hypotonia, hepatomegaly

Treatment: Avoid fasting. Supplementation with high energy carbohydrate drinks during periods of illness. Seek medical attention if these liquids are refused. Oral rehydration fluids are not adequate. If oral feedings are not possible, then intravenous fluids with concentrated dextrose should be started without waiting for symptoms of decompensation to develop.

Feed at least every three to four hours, including at night. Feeding intervals can be lengthened as the infant gets older.

Carnitine supplementation if low. Riboflavin trial.

### Special Considerations

***Fasting/infection/intercurrent illness*** - Parents must clearly understand that prolonged fasting and infection/intercurrent illnesses can cause serious complications in an infant with a fatty acid oxidation disorder. Infants experiencing stressful events such as trauma, infections/illnesses, and even receiving immunizations should be monitored to prevent metabolic decompensation.

## Medium/Short Chain 3-OH acyl CoA Dehydrogenase Deficiency (M/SCHAD)

Medium/Short chain 3-OH acyl Co-A dehydrogenase deficiency (M/SCHAD) is an inborn error of fatty acid oxidation. Infants may have poor feeding, vomiting and lethargy. Individuals with M/SCHAD are at risk for seizures, life threatening heart and breathing problems, coma and sudden death.

Inheritance: Autosomal recessive

Estimated Incidence: Unknown; thought to be very rare

**Abnormal Screen Result:** **Elevated C3DC (malonyl carnitine) + C4OH (3-OH butyryl carnitine)**

Method of Notification: All abnormal results are called to provider of record

**Next Steps if Abnormal:** **See infant as soon as possible to ascertain health status and repeat acyl carnitine profile on filter paper. Consult pediatric metabolic specialist for further instructions.**

Initiate treatment and diagnostic evaluation as recommended by specialist. **Report all findings to state newborn screening program.**

Neonatal Presentation: Poor feeding, vomiting, lethargy, seizures. Infants are at risk for metabolic decompensation/crisis, hypoglycemia. Plasma insulin may be elevated.

Treatment: Avoid fasting. Supplementation with high energy carbohydrate drinks during periods of illness. Seek medical attention if these liquids are refused. Oral rehydration fluids are not adequate.

If oral feedings are not possible, then intravenous fluids with concentrated dextrose should be started without waiting for symptoms of decompensation to develop.

Feed at least every three to four hours, including at night. May need cornstarch supplementation at bedtime to maintain blood glucose levels overnight. Carnitine supplementation if helpful.

Consider medication for infants with documented hyperinsulinism.

### **Special Considerations**

***Fasting/infection/intercurrent illness*** - Parents must clearly understand that prolonged fasting and infection/intercurrent illnesses can cause serious complications in an infant with a fatty acid oxidation disorder. Infants experiencing stressful events such as trauma, infections/illnesses, and even receiving immunizations should be monitored to prevent metabolic decompensation.

## Dienoyl Co-A Reductase Deficiency (DE RED)

2, 4-Dienoyl Co-A reductase deficiency (DE RED) is an inborn error of fatty acid oxidation. At least one infant with this disorder has been detected. This neonate presented with a short trunk, arms and fingers; microcephaly; hypotonia.

Inheritance: Autosomal recessive

Estimated Incidence: Unknown; thought to be extremely rare

**Abnormal Screen Result: Elevated C10:2 (decadienoyl carnitine)**

Method of Notification: All abnormal results are called to provider of record

**Next Steps if Abnormal: See infant as soon as possible to ascertain health status and repeat acyl carnitine profile on filter paper. Consult pediatric metabolic specialist for further instructions.**

Initiate treatment and diagnostic evaluation as recommended by specialist. **Report all findings to state newborn screening program.**

Neonatal Presentation: Hypotonia, possible ventricular septal defect, microcephaly

Treatment: Presumed treatment is same as that for other fatty acid metabolism disorders: Avoid fasting. Supplementation with high energy carbohydrate drinks during periods of illness.

Seek medical attention if these liquids are refused. Oral rehydration fluids are not adequate. If oral feedings are not possible, then intravenous fluids with concentrated dextrose should be started without waiting for symptoms of decompensation to develop.

Fat restricted diet with use of MCT oil as fat source. Carnitine if helpful. Feed at least every three to four hours, including at night.

### **Special Considerations**

***Fasting/infection/intercurrent illness*** - Parents must clearly understand that prolonged fasting and infection/intercurrent illnesses can cause serious complications in an infant with a fatty acid oxidation disorder. Infants experiencing stressful events such as trauma, infections/illnesses, and even receiving immunizations should be monitored to prevent metabolic decompensation.

## **Long Chain 3-OH Acyl Co-A Dehydrogenase Deficiency (LCHAD) and Trifunctional Protein Deficiency (TFP)**

Long chain 3-OH acyl Co-A dehydrogenase is one of three enzymes in LCAHD and trifunctional protein deficiency (TFP). Deficiencies of these enzymes overlap clinically. Affected persons may present with hypoketotic hypoglycemia, hepatic encephalopathy and muscle weakness usually associated with cardiomyopathy.

Other features include rhabdomyolysis, myoglobinuria and peripheral neuropathy. They may also show retinal pigmentation with vision loss in childhood. Symptoms may present as early as the first days of life.

Inheritance: Autosomal recessive

Estimated Incidence: Unknown

**Abnormal Screen Result: Primary Marker**  
**Elevated C16-OH (3-OH palmitoyl carnitine)**

**Secondary Markers**  
**Elevated C14:1 (tetradecenoyl carnitine)**  
**Elevated C14 (tetradecanoyl carnitine)**  
**Elevated C18 (octadecanoyl carnitine)**  
**Elevated C18:1-OH (3-OH oleyl carnitine)**

Method of Notification: All abnormal results as determined by the 4RS/CLIR Post-Analytical Tool are called to provider of record.

**Next Steps if Abnormal: See infant as soon as possible to ascertain health status and repeat acyl carnitine profile on filter paper. Consult pediatric metabolic specialist for further instructions.**

Initiate treatment and diagnostic evaluation as recommended by specialist. **Report all findings to state newborn screening program.**

Neonatal Presentation: Hypoketotic hypoglycemia. Some infants will have hepatic encephalopathy and muscle weakness associated with cardiomyopathy.

Treatment: Avoid fasting. Supplementation with high energy carbohydrate drinks during periods of illness. Seek medical attention if these liquids are refused. Oral rehydration fluids are not adequate. If oral feedings are not possible, then intravenous fluids with concentrated dextrose should be started without waiting for symptoms of decompensation to develop.

Feed at least every three to four hours, including at night. May need cornstarch supplementation via tube feeding overnight in older infancy/childhood.

Fat restricted diet with use of MCT oil as fat source. Essential fatty acid supplementation. DHA (docosahexaenoic acid) supplementation to prevent retinal degeneration may be used. Carnitine supplementation if helpful.

### **Special Considerations**

***Fasting/infection/intercurrent illness*** - Parents must clearly understand that prolonged fasting and infection/intercurrent illnesses can cause serious complications in an infant with a fatty acid oxidation disorder. Infants experiencing stressful events such as trauma, infections/illnesses, and even receiving immunizations should be monitored to prevent metabolic decompensation.

***HELLP syndrome*** is a life-threatening liver disorder thought to be a type of severe preeclampsia. It is characterized by *Hemolysis* (destruction of red blood cells), *Elevated Liver enzymes* (which indicate liver damage), and *Low Platelet count*.

About 10% to 20% of women who have severe preeclampsia develop HELLP where the fetus is affected by LCHAD. TFP is thought to be a less common cause of HELLP syndrome.

## Very Long Chain Acyl Co-A Dehydrogenase Deficiency (VLCAD)

Very long chain acyl Co-A dehydrogenase deficiency (VLCAD) is an inborn error of fatty acid oxidation. Infants may have hypoketotic hypoglycemia, hypotonia, hepatic dysfunction and cardiomyopathy. 20% of affected persons present as adolescents or adults with muscle fatigue, rhabdomyolysis and myoglobinuria triggered by exercise or fasting.

Inheritance: Autosomal recessive

Estimated Incidence: Unknown

**Abnormal Screen Result: Primary Markers**  
**Elevated C14:1 (tetradecenoyl carnitine)**  
**Elevated C14:1/C2 ratio**

**High Secondary Markers**  
**Elevated C12 (dodecanoyl carnitine)**  
**Elevated C12:1 (dodecenoyl carnitine)**  
**Elevated C14 (tetradecanoyl carnitine)**  
**Elevated C14:2 (tetradecadienoyl carnitine)**  
**Elevated C16 (palmitoyl carnitine)**

Method of Notification: All abnormal results are called to provider of record

**Next Steps if Abnormal: See infant as soon as possible to ascertain health status. A portion of the initial specimen will be sent to the Greenwood Genetic Center Laboratory for secondary testing. Consult pediatric metabolic specialist for further instructions.**

**Repeat acyl carnitine profile** as soon as possible on filter paper. Collection of other specimens may be indicated depending upon the results of secondary testing.

Initiate treatment and diagnostic evaluation as recommended by specialist. **Report all findings to state newborn screening program.**

Neonatal Presentation: Hypoketotic hypoglycemia, hepatic dysfunction, hypotonia and cardiomyopathy

Treatment: Avoid fasting. Supplementation with high energy carbohydrate drinks during periods of illness. Seek medical attention if these liquids are refused. Oral rehydration fluids are not adequate. If oral feedings are not possible, then intravenous fluids with concentrated dextrose should be started without waiting for symptoms of decompensation to develop.

Feed at least every three to four hours, including at night. May need cornstarch supplementation via tube feeding overnight in older infancy/childhood. Fat restricted diet with use of MCT oil as fat source. Essential fatty acid supplementation. Carnitine supplementation if helpful.

**Special Considerations**

***Fasting/infection/intercurrent illness*** - Parents must clearly understand that prolonged fasting and infection/intercurrent illnesses can cause serious complications in an infant with a fatty acid oxidation disorder. Infants experiencing stressful events such as trauma, infections/illnesses, and even receiving immunizations should be monitored to prevent metabolic decompensation.

## Glutaric Aciduria Type II (GA II)

Glutaric aciduria type II (GA II) is a fatty acid oxidation disorder caused by a deficiency of electron transfer flavoprotein (ETF) or ETF-ubiquinone oxidoreductase. These enzymes transfer electrons from the first step in  $\beta$ -oxidation to the electron transport chain.

There are three described types of GA II: neonatal onset with congenital anomalies, neonatal onset without congenital anomalies, and mild/late onset. Outcome for infants with GA II and congenital anomalies is extremely grave. This condition is also referred to as multiple acyl Co-A dehydrogenase deficiency (MADD).

Inheritance: Autosomal recessive

Estimated Incidence: Unknown

**Abnormal Screen Result: Primary Markers**  
**Elevated C4 (butyryl carnitine)**  
**Elevated C5 (isovaleryl carnitine)**

**Secondary Markers**  
**Elevated C6 (hexanoyl carnitine)**  
**Elevated C8 (octanoyl carnitine)**  
**Elevated C10 (decanoyl carnitine)**  
**Elevated C10:1**  
**Elevated C12**  
**Elevated C12:1**  
**Elevated C14**  
**Elevated C14:1 (tetradecenoyl carnitine)**  
**Elevated C16OH**

Method of Notification: All abnormal results are called to provider of record

**Next Steps if Abnormal: Potential medical emergency! See infant as soon as possible to ascertain health status and repeat acyl carnitine profile on filter paper. Consult pediatric metabolic specialist for further instructions.**

Initiate treatment and diagnostic evaluation as recommended by specialist. **Report all findings to state newborn screening program.**

Neonatal Presentation: Neonatal onset with congenital anomalies: prematurity, hypotonia, metabolic acidosis, cystic kidneys, facial dysmorphisms, rocker bottom feet.

Neonatal onset without congenital anomalies: hypotonia, tachypnea, metabolic acidosis, hypoglycemia, sweaty feet odor, cardiomyopathy

Treatment:

Neonatal onset with congenital anomalies: no treatment effective

Neonatal onset without congenital anomalies: treatment probably not effective

Mild/late onset—Avoid fasting. Supplementation with high energy carbohydrate drinks during periods of illness. Seek medical attention if these liquids are refused. Oral rehydration fluids are not adequate. If oral feedings are not possible, then intravenous fluids with concentrated dextrose should be started without waiting for symptoms of decompensation to develop.

Feed at least every three to four hours, including at night. May need cornstarch supplementation via tube feeding overnight in older infancy/childhood. May be prescribed diet restricted in fat, controlled in protein. Riboflavin supplementation if helpful.

### **Special Considerations**

***Fasting/infection/intercurrent illness*** - Parents must clearly understand that prolonged fasting and infection/intercurrent illnesses can cause serious complications in an infant with a fatty acid oxidation disorder. Infants experiencing stressful events such as trauma, infections/illnesses, and even receiving immunizations should be monitored to prevent metabolic decompensation.

## Carnitine Palmitoyl Transferase Type I Deficiency (CPT IA)

Carnitine palmitoyl transferase I (CPT IA) is necessary for the conversion of long chain fatty acyl Co-A molecules to their corresponding acylcarnitine molecules. Deficiency of this enzyme reduces the availability of acyl carnitines for transport into the mitochondrial matrix for fatty acid oxidation.

Inheritance: Autosomal recessive

Estimated Incidence: Unknown; thought to be more common in persons of Inuit or Hutterite (Germanic) origins

**Abnormal Screen Result: Primary High Markers**  
**Elevated C0**  
**Elevated C0 (Free Carnitine)/C16 (palmitoyl carnitine) + C18 (octadecanoyl carnitine) ratio**

**Primary Low Markers**  
**Low C16 (palmitoyl carnitine)**  
**Low C18 (octadecanoyl carnitine)**  
**Low C18:1**  
**Low C18:2**

Method of Notification: All abnormal results are called to provider of record

**Next Steps if Abnormal: Potential medical emergency! See infant as soon as possible to ascertain health status and repeat acyl carnitine profile on filter paper. Consult pediatric metabolic specialist for further instructions.**

**Initiate treatment and diagnostic evaluation as recommended by specialist. Report all findings to state newborn screening program.**

Neonatal Presentation: Seizures, hepatomegaly, hypoketotic hypoglycemia

Treatment: Avoid fasting. Supplementation with high energy carbohydrate drinks during periods of illness. Seek medical attention if these liquids are refused. Oral rehydration fluids are not adequate. If oral feedings are not possible, then intravenous fluids with concentrated dextrose should be started without waiting for symptoms of decompensation to develop.

Feed at least every three to four hours, including at night. Feeding regimen may be adjusted when the infant is older. May be prescribed diet restricted in fat. MCT oil may be used as a fat source after diagnosis is clearly established.

**Carnitine is contraindicated in treatment of CPT I.**

### **Special Considerations**

*Fasting/infection/intercurrent illness* - Parents must clearly understand that prolonged fasting and infection/intercurrent illnesses can cause serious complications in an infant with a fatty acid oxidation disorder. Infants experiencing stressful events such as trauma, infections/illnesses, and even receiving immunizations should be monitored to prevent metabolic decompensation.

*HELLP Syndrome/AFLP*: HELLP syndrome (hemolysis, elevated liver enzymes, low platelets)/AFLP (acute fatty liver of pregnancy) can occur in pregnancies where the fetus is affected by CPT I.

## Carnitine Palmitoyl Transferase Type II Deficiency (CPT II)

Carnitine palmitoyl transferase II deficiency (CPT II) is a disorder of fatty acid transport. In classic CPT II, the onset is during adolescence or early adulthood. It presents with muscle weakness, pain and myoglobinuria usually prompted by exercise, but sometimes by fasting, infection or stress. Renal failure from myoglobinuria occurs in 25% of affected persons.

The neonatal type, hepatocardiomyopathy CPT II, is extremely rare. Symptoms include hypoketotic hypoglycemia, hepatomegaly, skeletal muscle involvement and marked lipid accumulation in muscle. These infants may also have dysmorphic features.

Inheritance: Autosomal recessive

Estimated Incidence: Unknown

**Abnormal Screen Result: Primary Markers**  
**Elevated C16 (palmitoyl carnitine)**  
**Elevated C18**

**Informative Markers**  
**Elevated C12**  
**Elevated C16OH**  
**Elevated C18:1 (oleyl carnitine)**

Method of Notification: All abnormal results are called to provider of record

**Next Steps if Abnormal: Potential medical emergency! See infant as soon as possible to ascertain health status and repeat acyl carnitine profile on filter paper. Consult pediatric metabolic specialist for further instructions. Initiate treatment and diagnostic evaluation as recommended by specialist. Report all findings to state newborn screening program.**

Neonatal Presentation: Classic CPT II - none

Hepatocardiomyopathy CPT II: hypoketotic hypoglycemia, hepatomegaly, skeletal muscle involvement, marked lipid accumulation in muscle, dysmorphic features.

Treatment: Classic CPT II: Avoid fasting. Supplementation with high energy carbohydrate drinks during periods of illness. Seek medical attention if these liquids are refused. Oral rehydration fluids are not adequate. If oral feedings are not possible, then intravenous fluids with concentrated dextrose should be started without waiting for symptoms of decompensation to develop.

Feed at least every three to four hours, including at night. Feeding regimen may be adjusted when the infant is older. May be prescribed diet restricted in fat. MCT oil may be used as a fat source after diagnosis is clearly established.

Hepatocardiomyopathy CPT II: treatment probably not effective

**Special Considerations**

***Fasting/infection/intercurrent illness*** - Parents must clearly understand that prolonged fasting and infection/intercurrent illnesses can cause serious complications in an infant with a fatty acid oxidation disorder. Infants experiencing stressful events such as trauma, infections/illnesses, and even receiving immunizations should be monitored to prevent metabolic decompensation.

## Carnitine/Acylcarnitine Translocase Deficiency (CACT)

Carnitine/acylcarnitine translocase deficiency (CACT) is a disorder of fatty acid and carnitine transport. Two types have been described: one with neonatal onset and the other with onset later in infancy/early childhood.

In neonatal onset CACT, the affected infant presents with a metabolic crisis that often results in death from cardiopulmonary complications and/or liver failure. When the onset is later in infancy/early childhood, the affected person presents with hypoglycemia, but not cardiomyopathy.

Inheritance: Autosomal recessive

Estimated Incidence: Unknown, thought to be very rare

**Abnormal Screen Result: Primary Markers**  
**Elevated C16 (palmitoyl carnitine)**  
**Elevated C18 (octadecanoyl carnitine)**

**Informative Markers**  
**Elevated C12**  
**Elevated C16OH**  
**Elevated C18:1 (oleyl carnitine)**

Method of Notification: All abnormal results are called to provider of record

**Next Steps if Abnormal: Potential medical emergency! See infant as soon as possible to ascertain health status and repeat acyl carnitine profile on filter paper. Consult pediatric metabolic specialist for further instructions.**

**Initiate treatment and diagnostic evaluation as recommended by specialist. Report all findings to state newborn screening program.**

Neonatal Presentation: Neonatal onset CACT: hypoketotic hypoglycemia, hyperammonemia, hypotonia, liver dysfunction, cardiomyopathy

Later infancy/early childhood onset CACT: none

Treatment: Neonatal onset CACT: treatment probably not effective

Later infancy/early childhood onset CACT: Avoid fasting. Supplementation with high energy carbohydrate drinks during periods of illness. Seek medical attention if these liquids are refused. Oral rehydration fluids are not adequate. If oral feedings

are not possible, then intravenous fluids with concentrated dextrose should be started without waiting for symptoms of decompensation to develop.

Feed at least every three to four hours, including at night. Feeding regimen may be adjusted when the infant is older. May be prescribed diet restricted in fat. MCT oil may be used as a fat source after diagnosis is clearly established.

### **Special Considerations**

***Fasting/infection/intercurrent illness*** - Parents must clearly understand that prolonged fasting and infection/intercurrent illnesses can cause serious complications in an infant with a fatty acid oxidation disorder. Infants experiencing stressful events such as trauma, infections/illnesses, and even receiving immunizations should be monitored to prevent metabolic decompensation.

## Carnitine Uptake/Transport Deficiency (CUD)

In carnitine uptake/transport deficiency, carnitine transport across the plasma membrane is inhibited. The reduction in carnitine limits the formation of acylcarnitine and subsequently limits energy production. Skeletal and heart muscle tissues are particularly affected in this process.

Inheritance: Autosomal recessive

Estimated Incidence: 1:100,000

**Abnormal Screen Result: Low C0 (free carnitine)  
C3 (propionyl carnitine) + C16 (palmitoyl carnitine) < 2**

Method of Notification: All abnormal results where the sum of C3 (propionyl carnitine) and C16 (palmitoyl carnitine) is less than 2 are called to provider of record. Other low free carnitine results are mailed to the provider of record.

**Next Steps if Abnormal: Potential medical emergency when the free carnitine is low and the sum of C3 and C16 is less than 2! See infant as soon as possible to ascertain health status and repeat acyl carnitine profile on filter paper. Consult pediatric metabolic specialist for further instructions. Initiate treatment and diagnostic evaluation as recommended by specialist. Report all findings to state newborn screening program.**

Neonatal Presentation: Tachycardia, hepatomegaly, reduced muscle tone, poor feeding

Treatment: Carnitine supplementation. Avoid fasting. Supplementation with high energy carbohydrate drinks during periods of illness. Seek medical attention if these liquids are refused. Oral rehydration fluids are not adequate. If oral feedings are not possible, then intravenous fluids with concentrated dextrose should be started without waiting for symptoms of decompensation to develop.

Feed at least every three to four hours, including at night. Feeding regimen may be adjusted when the infant is older. May be prescribed diet restricted in fat.

### Special Considerations

**Fasting/infection/intercurrent illness** - Parents must clearly understand that prolonged fasting and infection/intercurrent illnesses can cause serious complications in an infant with a fatty acid oxidation disorder. Infants experiencing stressful events such as trauma, infections/illnesses, and even receiving immunizations should be monitored to prevent metabolic decompensation.

**Maternal CUD** - In some newborns, the low free carnitine is reflective of maternal CUD.