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_4. 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 biopterin cofactor biosynthesis and defects of biopterin cofactor regeneration.

Inheritance:	Autosomal recessive
Estimated Incidence:	PKU - 1:16,000 Benign hyperphenylalaninemia (H-PHE) - unknown Defects of biopterin 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 critical results are called to provider of record.
Next Steps if Abnormal:	**Repeat newborn screen** as soon as possible on filter paper. No formula/feeding change until results of repeat are known. If PHE is still markedly elevated in the repeat specimen, **refer to a pediatric metabolic specialist.** Further diagnostic evaluation may be necessary to rule out BH_4 defects. The metabolic specialist will initiate PHE restricted diet in coordination with a metabolic dietitian. **Report all findings to SC newborn screening program.**
Neonatal Presentation:	None.
Treatment:	PKU/defects of biopterin cofactor biosynthesis or regeneration: PHE restricted diet for life. Special metabolic formula is available to all SC residents (with a confirmed diagnosis) currently at no charge. BH_4 defects require additional diagnostic evaluation and treatment. Some persons with PKU are responsive to sapopterin, 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 restriction, 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 µM/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 (MET) - unknown, very rare
Abnormal Screen Result:	**Elevated MET** **Elevated MET/PHE**
Method of Notification:	All critical results are called to provider of record.
Next Steps if Abnormal:	**See infant as soon as possible** to ascertain health status and **repeat newborn screen** on filter paper. **Contact a pediatric metabolic specialist for further instructions**. Initiate treatment and diagnostic evaluation as recommended by specialist. **Report all findings to SC 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. Special metabolic formula is available to all SC residents (with a confirmed diagnosis) currently at no charge.

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 delayed physical and intellectual 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 and 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. Contact pediatric metabolic specialist for further instructions.** Initiate treatment and diagnostic evaluation as recommended by specialist. **Report all findings to SC 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 metabolic formula is available to all SC residents, currently at no charge.

Special Considerations

Fasting/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 (UCD) caused primarily by a deficiency of the enzyme Argininosuccinic acid synthetase. In addition to elevated citrulline, these conditions are associated with hyperammonemia which may be severe and life-threatening. 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 UCD. 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.

Other rarer UCD are pyruvate carboxylase deficiency, Ornithine trans-carbamylase deficiency (OTC), and Carbamoyl-phosphate synthase deficiency (CPS).

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 or CIT/ARG ratio**
Method of Notification:	All critical results are called to provider of record.
Next Steps if Abnormal:	**Potential medical emergency! See infant as soon as possible to ascertain health status. Contact a 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 SC 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 metabolic

formula is available to all SC residents (with a confirmed diagnosis) currently at no charge.

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: **Additional marker:**	**Elevated CIT or ASA** **CIT/ARG or ASA/ARG ratio**
Method of Notification:	All critical results are called to provider of record.
Next Steps if Abnormal:	**Potential medical emergency! See infant as soon as possible to ascertain health status. Contact a 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 SC 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.

Argininemia (ARG) - *NEW*

Argininemia (aka) Arginase deficiency is a very rare secondary newborn screening finding. It results from inherited defects in arginase, an enzyme in the urea cycle that helps convert ammonia to urea. Arginase deficiency leads to elevated plasma arginine and in some cases, hyperammonemia. Presentation in the neonatal period is rare.

Clinical Considerations: Neonates with argininemia are usually asymptomatic but can develop mild to moderate hyperammonemia once receiving dietary protein. Later signs include developmental delay, seizures, and lower extremity spasticity. Rarely, argininemia may cause severe neonatal illness as seen in the other urea cycle disorders.

Inheritance:	Autosomal recessive
Estimated Incidence:	1 in 300,000 to 1 in 1,000,000
Neonatal Presentation:	Usually none.
Abnormal Screen Result:	**Elevated ARG *and* ARG/ORN ratio**
Method of Notification:	All abnormal ARG/ORN results are called and sent to the provider of record. Elevated ARG (only) results are available to the provider of record in eReports.
Next Steps if Abnormal:	**See infant as soon as possible to ascertain health status and repeat newborn screen on filter paper. Contact a pediatric metabolic specialist for further instructions.**

Initiate treatment and diagnostic evaluation if recommended by specialist. Report all findings to SC Newborn Screening Program.

Treatment:	Patients are treated with nitrogen scavengers, severe restriction of natural protein, and essential amino acids supplementation. Enzyme replacement has also been used successfully.

Tyrosinemia

Tyrosinemia I (TYR I) is caused by a deficiency in the enzyme fumarylacetoacetase. Untreated infants are at risk for liver failure, jaundice, delayed growth, 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 µM 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 newborn screen** on filter paper. **Contact a pediatric metabolic specialist for further instructions.** Initiate treatment and diagnostic evaluation as recommended by specialist. **Report all findings to SC 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 galctose-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 classic 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 mild variant form of galactosemia called **Duarte galactosemia**. Almost all cases of Duarte 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 SC 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. Contact a pediatric metabolic specialist for further instructions and diagnostic evaluation.

If GALT is normal in the initial specimen, repeat galactosemia screening as soon as possible. THERE IS 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, contact a 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.

Pompe Disease (aka)
Glycogen Storage Disease Type II

Pompe disease is a lysosomal storage disorder (LSD) caused by a defect in the acid alpha-glucosidase (GAA) gene, resulting in glycogen accumulation, primarily in cardiac and skeletal muscle.

Pompe is an inherited condition that affects many different parts of the body. It is considered a lysosomal storage disorder (LSD) because people with Pompe have lysosomes (the recycling centers of each cell) that cannot break down certain types of complex sugars. This causes undigested sugar and other harmful substances to build up in cells throughout the body, resulting in a variety of symptoms.

There are three forms of Pompe Disease (classic infantile onset, non-classic infantile onset, and late onset), which differ in regard to disease severity and age of onset. The symptoms and long-term outcome of each form also vary widely.

Inheritance:	Autosomal recessive
Estimated Incidence:	1:40,000 (general population) 1:14,000 (African American population)
1st tier screen:	**Low to absent GAA enzyme**
2nd tier screen:	***GAA* molecular sequencing**
Method of Notification:	All 1st tier screening results with a low to absent GAA are sent to the provider of record. Sample will be sent to reference lab for 2nd tier molecular testing.
Next Steps if Abnormal:	**Potential medical emergency when GAA is very low or absent.** See infant as soon as possible to ascertain health status. Report all subsequent findings to SC Newborn Screening program.

NOTE: a lower than expected GAA can be found in babies who do not have Pompe Disease, ex. infants with Pseudo deficiency alleles or Pompe carriers. However, prompt evaluation is advised, as a precaution.

Neonatal Presentation:	Hypotonia, progressive weakness, macroglossia, and hepatomegaly are common symptoms of the infantile form. The heart is also characteristically affected.

Treatment:

Enzyme replacement therapy (ERT) is available for all forms of Pompe disease and should only be given under the guidance of a metabolic specialist. ERT should be started as soon as possible

for patients with the infantile form after evaluating cross-reacting immunological material (CRIM) status and determining if immune modulation is appropriate.

Physical Therapy
Physical therapy will be necessary to help infants, children, and adolescents develop motor skills, maintain range of motion, and strengthen muscles and joints.

Respiratory Therapy
Because lung infections, breathing difficulties and heart enlargement are common in children with Pompe, consultation with a pulmonologist and/or cardiologist may be needed.

Dietary Treatments
Many babies with Pompe have trouble feeding and gaining weight. Some children with Pompe are managed on a soft diet, while others may require a feeding tube.

***Special Considerations*:**

Clinical evaluation is needed to distinguish Infantile Onset Pompe Disease (IOPD) from Late Onset Pompe Disease (LOPD). Assessment should include physical, pulmonology, and cardiac (CXR/EKG/ECHO) evaluations, as well as ancillary enzymology (CK, LDH, AST, ALT).

Mucopolysaccharidosis type 1 (MPS I)

Mucopolysaccharidosis type 1 (MPS I) also known as Hurler's disease, is an autosomal recessive lysosomal storage disorder (LSD) caused by pathogenic variants in the IDUA (alpha-L-iduronidase) gene, leading to deficient alpha-L-iduronidase activity.

This deficiency leads to the accumulation of glycosaminoglycans (also known as GAGs or mucopolysaccharides) in the lysosomes, resulting in cellular dysfunction.

MPS I is also historically and collectively known as Hurler syndrome, Hurler-Scheie syndrome, and Scheie syndrome. There is wide variability in severity and age of onset.

Inheritance:	Autosomal recessive
Estimated Incidence:	Approx. 1 in 100,000
1st tier screen:	**Low to absent IDUA enzyme**
2nd tier screen:	***IDUA* molecular sequencing**
Method of Notification:	All 1st tier screening results with a low to absent IDUA are sent to the provider of record. Sample will be sent to reference lab for 2nd tier molecular testing.
Next Steps if Abnormal:	See infant as soon as possible to ascertain health status. Report all subsequent findings to SC Newborn Screening program.
Neonatal Presentation:	Clinical presentation and severity of MPS I ranges from severe to attenuated. Clinical features may include coarse facies, hepatosplenomegaly, progressive dysostosis multiplex, cardiac valvular disease, umbilical hernia, corneal clouding, hearing loss, and developmental delay.

NOTE: a lower than expected IDUA can be found in babies who do not have MPS I, ex. infants with Pseudo deficiency alleles or MPS I carriers. However, prompt evaluation is advised, as a precaution.

Treatment:

Treatment options include hematopoietic stem cell transplantation, enzyme replacement therapy (ERT), and emerging therapies. Ongoing multi-specialty care is necessary. ERT administration should only be given under the guidance of a specialist with expertise in treatment of lysosomal storage disorders.

Physical therapy is a very important part of treating the signs and symptoms of MPS I. Early and consistent physical therapy can help preserve mobility and lessen pain and joint stiffness.

Special Considerations

Select surgeries may improve the child's quality of life. Removal of the tonsils, adenoids, and insertion of ear ventilation tubes (vent tubes) can prevent some upper respiratory infections that may reduce hearing loss. Hearing aids may be recommended for some individuals.

Children with mild to severe MPS I may develop a buildup of fluid in the brain (hydrocephaly). A surgery to relieve the pressure inside the skull may be recommended.

Krabbe Disease - *NEW*

Krabbe disease (aka globoid cell leukodystrophy) is a lysosomal disorder caused by deficiency of galactocerebrosidase (GALC). The disorder results in impaired turnover of myelin with subsequent dysfunction and eventual loss of oligodendrocytes and Schwann cells.

There are multiple forms of Krabbe disease. The infantile form usually presents before the first year of life. Newborns are asymptomatic. If left untreated, survival beyond 2 years of age is uncommon**.**

1st tier screen:	Low to absent GALC enzyme
2nd tier screen:	**Elevated Psychosine (PSY)**
3rd tier test:	**Abnormal *GALC* molecular sequencing**

Differential Diagnosis: Saposin A deficiency

NOTE: Decreased enzyme activity is suggestive of Krabbe disease. However, this result alone does not exclude pseudo-deficiency or carriers, who may exhibit decreased enzyme levels **without** disease.

Combined evaluation of GALC activity **and** psychosine concentration predict the phenotype (unaffected vs. early vs. late onset Krabbe disease). Molecular genetic testing can confirm the diagnosis.

Method of Notification: All **elevated** 2nd tier PSY results are called and sent to the provider of record. Abnormal screening samples will be further reflexed for 3rd tier molecular testing. All other results are available via eReports.

Next steps if abnormal:

See infant as soon as possible to ascertain health status. **If psychosine is elevated, contact a pediatric metabolic and/or transplant specialist immediately for further instructions.** Report all subsequent findings to the SC Newborn Screening program.

Presentation and Treatment:

The clinical presentation of Krabbe disease ranges from a rapidly progressive infantile form to more slowly progressive later-onset variants. All forms of Krabbe disease are associated with leukodystrophy. But the age of onset and rate of progression vary widely.

The only available therapy for Krabbe is hematopoietic stem cell transplantation*. It is most effective if performed before 30 days of life in patients with the infantile form, or prior to the onset of clinical symptoms in later-onset forms.

*Gene therapy and other clinical trials may be available.

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, C3/C16, or C3/MET ratios**
Method of Notification:	All results where the C3 is greater than 10 μM 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 μM 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 μM and the C3/C2 and/or C3/C16 is elevated or when the C3 is greater than 15 μM, regardless of the ratio levels.** See infant as soon as possible to ascertain health status. Contact a 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 SC 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 metabolic formula is available to all SC residents (with a confirmed diagnosis) currently at no charge.

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 + C4OH/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 newborn screen** on filter paper. **Contact a pediatric metabolic specialist for further instructions**. Initiate treatment and diagnostic evaluation as recommended by specialist. **Report all findings to SC 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 & Cobalamin 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, C3/C16** **Elevated C3/C0 or C3/MET**
Method of Notification:	All results where the C3 is greater than 10 μM 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 μM 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 μM and the C3/C2 and/or C3/C16 is elevated or when the C3 is greater than 15 μM regardless of the ratio levels.** See infant as soon as possible to ascertain health status. Contact a 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 SC 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 (Cobalamin C, D, or F) are rare types of methylmalonic acidemia. Individuals with these forms of methylmalonic acidemia have trouble producing certain cobalamin enzymes, which cause harmful levels of homocysteine and methylmalonic acid to build up in their bodies.

Abnormal Screen Result: **Elevated C3 (propionyl carnitine)**
Elevated C3/MET (Methionine) ratio
Elevated C3/C2 or C3/C16 ratios

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

Infants with Cobalamin 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 Cobalamin 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 (IBG) is a disorder of valine metabolism. Infants with this rare secondary disorder may have cardiomyopathy and anemia. **Note: This disorder may be detected but not reported due to universal screening of other disorders.**

Inheritance:	Presumed autosomal recessive
Estimated Incidence:	Unknown; thought to be very rare
Abnormal Finding:	Elevated C4 (butyryl carnitine)
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 newborn screen on filter paper. Contact a pediatric metabolic specialist for further instructions.** **Initiate treatment and diagnostic evaluation as recommended by specialist**. **Report all findings to SC 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 newborn screen** on filter paper. **Contact a pediatric metabolic specialist for further instructions.** Initiate treatment and diagnostic evaluation as recommended by specialist. **Report all findings to SC 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 newborn screen** on filter paper. **Contact a pediatric metabolic specialist for further instructions.** Initiate treatment and diagnostic evaluation as recommended by specialist. **Report all findings to SC 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 (βKT) 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 C5:1 (tiglyl carnitine)** **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 newborn screen** on filter paper. **Contact a pediatric metabolic specialist for further instructions.** Initiate treatment and diagnostic evaluation as recommended by specialist. **Report all findings to SC 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 newborn screen** on filter paper. **Contact a pediatric metabolic specialist for further instructions**. Initiate treatment and diagnostic evaluation as recommended by specialist. **Report all findings to SC 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) as 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)** **Elevated C6DC**
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 newborn screen** on filter paper. **Contact a pediatric metabolic specialist for further instructions.** Initiate treatment and diagnostic evaluation as recommended by specialist. **Report all findings to SC 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 may have speech and language delay, 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
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 newborn screen** on filter paper. **Contact a pediatric metabolic specialist for further instructions**. Initiate treatment and diagnostic evaluation as recommended by specialist. **Report all findings to SC newborn screening program**.
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 newborn screen** on filter paper. **Contact a pediatric metabolic specialist for further instructions**. Initiate treatment and diagnostic evaluation as recommended by specialist. **Report findings to SC 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 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. Contact a pediatric metabolic specialist for further instructions. A portion of the initial specimen will be sent to the Greenwood Genetic Center (GGC) Laboratory for secondary testing.** **Repeat newborn screen** 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 SC 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 Marker** **Elevated C8 (octanoyl carnitine)** **Secondary Markers** **Elevated C6 (hexanoyl carnitine)** **Elevated C10 (decanoyl carnitine)** **Elevated C10:1 (decenoyl 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 newborn screen on filter paper. Contact a pediatric metabolic specialist for further instructions**. Initiate treatment and diagnostic evaluation as recommended by specialist. **Report all findings to SC 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 Co-A Thiolase Deficiency (MCAT)

Medium chain ketoacyl Co-A 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)** **Elevated C10 (decanoyl 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. **Contact a pediatric metabolic specialist for further instructions.** Initiate treatment and diagnostic evaluation as recommended by specialist. **Report all findings to SC 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 a secondary inborn error of fatty acid oxidation. Outcomes in affected persons have been quite variable. Infants may have seizures, poor feeding, progressive muscle weakness, developmental delay, and hypotonia.

Note: This rare disorder may be detected but not reported due to universal screening of other disorders.

Inheritance:	Autosomal recessive
Estimated Incidence:	1:40,000 to 1:100,000
Abnormal Finding:	Elevated C4 (butyryl carnitine)
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 newborn screen on filter paper. Contact a pediatric metabolic specialist for further instructions**. Initiate treatment and diagnostic evaluation as recommended by specialist. **Report all findings to SC 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 hyper-insulinisum.

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 newborn screen on filter paper. Contact a pediatric metabolic specialist for further instructions**. Initiate treatment and diagnostic evaluation as recommended by specialist. **Report all findings to SC 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 Markers** **Elevated C16OH (3-OH palmitoyl carnitine)** **Elevated C18OH** **Secondary Markers** **Elevated C14:1 (tetradecenoyl carnitine)** **Elevated C14 (tetradecanoyl carnitine)** **Elevated C14OH** **Elevated C18 (octadecanoyl carnitine)** **Elevated C18OH/C18 ratio** **Elevated C18:1-OH (3-OH oleyl carnitine)** **Elevated C18:2-OH**
Method of Notification:	All abnormal results as determined by the 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 newborn screen on filter paper. Contact a pediatric metabolic specialist for further instructions**. Initiate treatment and diagnostic evaluation as recommended by specialist. **Report all findings to SC 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 *H*emolysis (destruction of red blood cells), *E*levated *L*iver enzymes (which indicate liver damage), and *L*ow *P*latelet 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** **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 (GGC) Laboratory for secondary testing. Contact a pediatric metabolic specialist for further instructions**. **Repeat newborn screen** 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 SC 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 metabolic formula is available to all SC residents (with a confirmed diagnosis) currently at no charge.

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 β-oxidation to the electron transport chain.

There are 3 described types of GA II: neonatal onset with congenital anomalies, neonatal onset without congenital anomalies, and mild/late onset. The outcome for infants with GA II and congenital anomalies is extremely grave. This condition has also been 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** **Elevated C18**
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 newborn screen on filter paper. Contact a pediatric metabolic specialist for further instructions.** Initiate treatment and diagnostic evaluation as recommended by specialist. **Report all findings to SC 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 effective treatment. 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 1A)

Carnitine palmitoyl transferase 1 (CPT 1A) 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 (Free Carnitine)** **Elevated C0/C16 + C18 ratio** **Elevated C3/C16** **Primary Low Markers** **Low C18:2, C18:1, C18 or C16**
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. A portion of the initial specimen will be sent to the Greenwood Genetic Center (GGC) Laboratory for secondary testing.** **Contact a pediatric metabolic specialist for further instructions. Initiate treatment and diagnostic evaluation as recommended by specialist. Report all findings to SC 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 1A.

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 1.

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, hepatocardiomuscular 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** **Low C3** **Elevated C16 and/or C18:1** **Other Informative Markers** **Elevated C14** **Elevated C18:2** **Elevated C18** **Low C3/C16**
Method of Notification:	All abnormal results are called to the provider of record.
Next Steps if Abnormal:	**Potential medical emergency! See the infant as soon as possible to ascertain health status and repeat newborn screen on filter paper.** **Contact a pediatric metabolic specialist for further instructions. Initiate treatment and diagnostic evaluation as recommended by specialist. Report all findings to SC newborn screening program**.
Neonatal Presentation:	Classic CPT II - none Hepatocardiomuscular 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.

Hepatocardiomuscular CPT II: treatment may not be 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** **Low C3** **Elevated C16 and/or C18:1** **Other Informative Markers** **Elevated C14** **Elevated C18:2** **Elevated C18** **Low C3/C16**
Method of Notification:	All abnormal results are called to the provider of record.
Next Steps if Abnormal:	**Potential medical emergency! See the infant as soon as possible to ascertain health status and repeat newborn screen on filter paper. Contact a pediatric metabolic specialist for further instructions.** **Initiate treatment and diagnostic evaluation as recommended by specialist. Report all findings to SC newborn screening program**.
Neonatal Presentation:	Neonatal onset CACT: hypoketotic hypoglycemia, hypotonia, hyperammonemia, 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)
aka Primary carnitine deficiency

In carnitine uptake/transport deficiency (aka) Primary carnitine 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 in general population 1:40,000 in Japanese
Abnormal Screen Results:	**Low C0 (free carnitine) and** **C3 (propionyl carnitine) + C16 (palmitoyl carnitine) < 2** **Other Informative markers** **Low C2, Low C16, Low C18:2, C18:1, or C18**
Method of Notification:	All abnormal results where the sum of C3 and C16 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 the infant as soon as possible to ascertain health status and repeat newborn screen on filter paper.** **Contact a pediatric metabolic specialist for further instructions. Initiate treatment and diagnostic evaluation as recommended by specialist. Report all findings to SC 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.

****Inheritance*** - Systemic primary carnitine deficiency is an autosomal recessive disease caused by mutations in the *SLC22A5* gene. An individual who inherits one copy of a *SLC22A5* gene mutation is a carrier. Carriers are not expected to have related health problems but may show some signs and symptoms related to the condition.

An individual who inherits two *SLC22A5* mutations, one from each parent, is expected to be affected with systemic primary carnitine deficiency.

Maternal CUD - In some newborns, the low free carnitine (C0) is reflective of maternal CUD.

Carriers of fatty-acid oxidation defects, including primary carnitine deficiency, do not typically show symptoms of the disease. However, there may be an increased risk of serious pregnancy complications, particularly in the third trimester, in women carrying a fetus affected with a fatty-acid oxidation defect.

A woman whose pregnancy may be affected by a fatty-acid oxidation defect, such as primary carnitine deficiency, should speak with her physician for recommendations and may benefit from consultation with a high-risk physician.