



Newborn Screening Program

**REFERENCE**  
**GUIDE** *of*  
**GENETIC**  
**DISORDERS**



The Georgia Department of Public Health (DPH) Newborn Screening (NBS) program is legislatively mandated to provide early detection of inherited genetic disorders aimed to reduce morbidity and mortality attributed to these disorders.

NBS serves a vital public health function to identify at-risk infants in the first few days of life so that early intervention can be implemented to prevent severe intellectual disability, chronic disability, or death.

Left untreated, the cost of these disorders is enormous in terms of human suffering and economic impact. Georgia law (O.C.G.A. 31-12-6 and O.C.G.A. 31-12-7) directs a statewide network for genetic services be developed as a cooperative effort between public health, appropriate medical centers, and private practitioners.

**NBS Program Office**

(404) 657-4143

**Augusta University (AU) Hemoglobin Follow-Up**

(706) 721-6251 or MD On-Call (706) 721-5600

**Georgia Public Health Laboratory**

(404) 327-7950

**CHOA Hemoglobin Follow-Up**

(404) 785-1087 or MD On-Call (470) 565-3425

**Emory Genetics Follow-Up**

(404) 778-8560

**SCFGa Hemoglobin Traits/Carriers Follow-Up**

(404) 755-1541 or (800) 326-5287

# AMINO ACID DISORDERS

## **Argininosuccinic Aciduria (ASA) 1:70,000**

*Deficiency of Argininosuccinate lyase in urea cycle.*

**Primary Indicator:** Elevated citrulline.

**Symptoms:** Progressive lethargy, loss of appetite, irritability, vomiting, hypothermia, respiratory alkalosis, hepatic disease, hyperammonemia, coma, seizures, apnea, intellectual disability or death.

**Treatment:** High-caloric, protein-restrictive diet, arginine supplementation, medical foods, ammonia scavenging drugs.

## **Citrullinemia (CIT) (Type I) 1:57,000 babies born in U.S. (Type II) 1:200,000**

*Deficiency in argininosuccinic acid synthetase in urea cycle.*

**Primary Indicator:** Elevated citrulline.

**Symptoms:** Progressive lethargy, loss of appetite, vomiting, hypothermia, respiratory alkalosis, coma, seizures, apnea, intellectual disability or death.

**Treatment:** High-caloric, protein-restrictive diet, arginine supplementation, medical foods, ammonia scavenging drugs.

# AMINO ACID DISORDERS

## **Homocystinuria 1:200,000-300,000**

*Deficiency of cystathioine synthetase, unable to metabolize methionine and homocystine.*

**Primary Indicator:** Elevated methionine.

**Symptoms:** Intellectual disability, seizures, behavior disorder, thromboses, dislocated lenses, tall/thin stature.

**Treatment:** Life-long low methionine diet with cysteine supplementation. Pyridioxine supplementation also if responsive. Special formulas and medical foods, and treatment with Betaine (cystadane).

## **Maple Syrup Urine Disease (MSUD) 1:185,000**

*Deficiency of the branched-chain alpha-keto acid dehydrogenase (BCKD) enzyme complex, unable to metabolize the branched chain amino acids (leucine, isoleucine, and valine).*

**Primary Indicator:** Elevated branch chain amino acids (Leucine).

**Symptoms:** Acidosis, hypertonia, seizures, vomiting, apnea, coma, severe intellectual disability, neurological impairment, death. Ear wax/urine smells like maple syrup.

**Treatment:** Life-long diet low in leucine, isoleucine and valine. Thiamine supplementation if responsive. Special formulas and medical foods.

# AMINO ACID DISORDERS

## **Phenylketonuria (PKU) 1:10,000-15,000**

*Deficiency of phenylalanine hydroxylase, unable to convert phenylalanine to tyrosine.*

**Primary Indicator:** Elevated phenylalanine.

**Symptoms:** Severe intellectual disability, eczema, seizures, decreased pigmentation, behavior disorder, "mousey" odor.

**Treatment:** Life-long low phenylalanine diet, tyrosine supplementation. Special formulas and medical foods.

## **Tyrosinemia 1:100,000**

*Deficiency of Fumarylacetoacetate hydrolase (FAH), unable to metabolize tyrosine other variant forms.*

**Primary Indicator:** Elevated tyrosine.

**Symptoms:** Hepatic damage, liver cirrhosis and failure, Fanconi syndrome, poor growth, hepatomegaly, hepatic carcinoma, thrombocytopenia.

**Treatment:** Life-long low phenylalanine and tyrosine diet. Special formulas and medical foods. Orfadin© is used to prevent liver and kidney damage.

# FATTY ACID OXIDATION DISORDERS

## **Carnitine uptake defect (Group of disorders including CPT I, II, translocase) 1:100,000**

*Deficiency in Carnitine transporters.*

**Primary Indicator:** Low C0.

**Symptoms:** Extreme sleepiness, irritable mood, poor appetite. Progressive hypokinetic dilated cardiomyopathy that is generally associated with muscular weakness. Coma or sudden death can also occur.

**Treatment:** Avoidance of fasting, dietary supplementation with medium chain triglycerides. Do not give intralipids or MCT oil to these patients.

## **Long Chain 3 hydroxyl acyl-CoA Dehydrogenase Deficiency (LCHAD)\***

*Enzyme deficiency that breaks down long-chain fatty acids .*

**Primary Indicator:** Elevated C 16-OH and C18: 1OH.

**Symptoms:** Hypoglycemia, lethargy, failure to thrive, and developmental delay, often accompanied by hypotonia and cardiomyopathy. Some SIDS cases are caused by LCHAD.

**Treatment:** Avoid fasting and follow high-carbohydrate diet. Special formulas and medical foods. MCT oil supplementation.

*\* It is currently unknown the exact number of infants affected by LCHAD*

# FATTY ACID OXIDATION DISORDERS

## Medium Chain acyl-CoA Dehydrogenase Deficiency (MCAD) 1:15,000

*Enzyme deficiency, unable to metabolize fat for energy in the absence of glucose.*

**Primary Indicator:** Elevated C8.

**Symptoms:** Hypoglycemia, hyperammonemia, vomiting, lethargy, coma, apnea, cardiac arrest, sudden unexplained death.

**Treatment:** Regular feedings to avoid fasting, low fat diet, oral L-carnitine supplementation.

## Trifunctional Protein Deficiency (TFP)\*\*

*Deficiency of Trifunctional protein involved in mitochondrial long chain fatty acid oxidation.*

**Primary Indicator:** Elevated C16-OH and C18: 1OH.

**Symptoms:** Hypoketotic hypoglycemia in infancy or early childhood, along with hypotonia and often fatal hypertrophic cardiomyopathy, or sudden unexplained death.

**Treatment:** Low fat, high carbohydrate diet. Avoid fasting and may require L-carnitine and MCT oil supplementation. Special formulas and medical foods.

*\*\* Rare, exact number of individuals affected by TFP is currently unknown.*

# FATTY ACID OXIDATION DISORDERS

## **Very Long-Chain acyl-CoA Dehydrogenase Deficiency (VLCAD)\*\*\***

*Deficiency of enzyme that breaks down very long-chain fatty acids.*

**Primary Indicator:** Elevated C14: 1 (long-chain fatty acid).

**Symptoms:** Hypoketotic hypoglycemia, hepatocellular disease, cardiomyopathy, fatal infantile encephalopathy.

**Treatment:** Avoid fasting. Dietary supplements with MCT oil. Possible carnitine supplements.

\*\*\* *The exact number affected by VLCAD is currently unknown. Some estimates 1:30,000*



# ORGANIC ACID DISORDERS

## **Beta-Ketothiolase Deficiency (BKT)\***

*Deficiency of mitochondrial acetoacetyl-CoA thiolase in isoleucine pathway.*

**Primary Indicator:** Elevated C5: 1 and C5-OH.

**Symptoms:** Some are asymptomatic, while others have episodes of severe metabolic acidosis and ketosis. Vomiting, poor appetite, tiredness, fever, and trouble breathing.

**Treatment:** L-Carnitine supplementation, avoid fasting, low protein diet, monitor urinary ketones.

## **Glutaric Acidemia type I (GA1) 1:40,000**

*Deficiency of Glutaryl-CoA dehydrogenase in Lysine, Hydroxylsine, and Tryptophan pathway.*

**Primary Indicator:** Elevated C5-DC.

**Symptoms:** Hypoglycemia, rigidity of muscles, uncoordinated movements, vomiting, metabolic acidosis, hypotonia, seizures and central nervous system degeneration.

**Treatment:** Carnitine supplementation. Restriction of dietary lysine and tryptophan. IV fluids and bicarbonate used to treat acidosis. Special formulas and medical foods.

*\* Incidence Unknown estimated to affect fewer than one in one million newborns.*

# ORGANIC ACID DISORDERS

## **3-OH 3-CH3 Glutaric Aciduria (HMG) (HMG-CoA lyase deficiency)\***

*Deficiency of 3-Hydroxy-3-methylglutaryl-CoA lyase deficiency in leucine pathway and in ketone body synthesis.*

**Primary Indicator:** Elevated C6DC and C5-OH.

**Symptoms:** Severe hypoglycemia, metabolic acidosis, hyperammonemia, vomiting, hypotonia, coma, and death.

**Treatment:** L-Carnitine supplementation, avoid fasting, restriction of dietary protein and fat. Medical foods.

## **Isovaleric Acidemia (IVA) 1:230,000**

*Deficiency of Isovaleryl-CoA dehydrogenase, unable to metabolize leucine.*

**Primary Indicator:** Elevated C5.

**Symptoms:** Vomiting, acidosis, ketosis, mild hyperammonemia, hypocalcemia, transient bone marrow suppression, lethargy, coma. "Sweaty feet" odor.

**Treatment:** Life-long restriction of dietary protein, L-Carnitine supplementation. Special formulas and medical foods.

*\* Rare, one estimate is that there have been fewer than 100 cases worldwide.*

# ORGANIC ACID DISORDERS

## **3-Methylcrotonyl-CoA Carboxylase Deficiency (3MCC) 1:36,000-50,000**

*Deficiency of 3-methylcrotonyl-CoA carboxylase in Leucine pathway.*

**Primary Indicator:** Elevated C5-OH.

**Symptoms:** Can be asymptomatic, or can have symptoms including acute metabolic acidosis, hypoglycemia, hypotonia, muscle atrophy, seizures and dermatologic changes.

**Treatment:** L-Carnitine supplementation and restriction of dietary protein. Special formulas and medical foods.

## **Multiple Carboxylase Deficiency (MCD) (Holocarboxylase Deficiency) 1:87,000**

*Deficiency of biotin, part of the vitamin B complex.*

**Primary Indicator:** Elevated C5-OH.

**Symptoms:** Seizures, hypotonia, immune system impairment, skin rashes, hair loss, hearing loss, and intellectual disability.

**Treatment:** Biotin supplementation.

# ORGANIC ACID DISORDERS

## **Methylmalonic Acidemias (Mutase Deficiency or Cbl A,B) 1:50,000 to 1:100,000**

*Deficiency of Methylmalonyl-CoA mutase required in the oxidation of amino acids.*

**Primary Indicator:** Elevated C3.

**Symptoms:** Neonatal metabolic acidosis and ketosis with hyperammonemia, lethargy, failure to thrive, vomiting, respiratory distress, hypotonia, and can develop chronic renal failure.

**Treatment:** Restriction of isoleucine, methionine, valine, and threonine. L-Carnitine supplementation. Vitamin B-12 treatment. Special formulas and medical foods.

## **Propionic Acidemia (PROP) 1:35,000 to 75,000**

*Deficiency of Propionyl-CoA carboxylase.*

**Primary Indicator:** Elevated C3.

**Symptoms:** Neonatal severe metabolic acidosis and ketosis with hyperammonemia, refusal to feed, vomiting, lethargy, hypotonia, developmental delay, seizures and death.

**Treatment:** L-Carnitine supplementation and restriction of methionine, valine, isoleucine, and threonine. Special formulas and medical foods.

# LYSOMAL STORAGE DISORDERS

## **Mucopolysaccharidosis I (MPS I) 1:100,000 Attenuated form: 1:500,000**

*Deficiency of lysosomal enzyme  $\alpha$ -L-iduronidase (IDUA).*

**Primary Indicator:** Complete or partial deficiency of enzyme activity.

**Symptoms:** Umbilical or inguinal hernia, macrocephaly, distinctive facial features that appear "coarse". Varying degrees of developmental delay and learning disabilities. Hepatomegaly, splenomegaly, corneal clouding, hearing loss, frequent "running nose".

**Treatment:** Symptomatic and palliative therapies. Enzyme replacement therapy (ERT) with recombinant alpha-L-iduronidase. Early Hematopoietic stem cell transplantation (HSCT).

## **Pompe Disease 1:40,000**

*Deficiency of lysosomal enzyme acid alpha- glucosidase (GAA).*

**Primary Indicator:** Complete or partial deficiency of enzyme activity.

**Symptoms:** Hypotonia, myopathy. Failure to grow, failure to thrive. Difficulty breathing, trouble feeding, respiratory infections, hearing problems.

**Treatment:** Enzyme replacement therapy (ERT) with recombinant alpha-glucosidase. Physical therapy, respiratory therapy.

# ENDOCRINE DISORDERS

## **Congenital Adrenal Hyperplasia (CAH) 1:15,000**

*Deficiency of 21-hydroxylase, unable to make cortisol and aldosterone. Many variant forms exist.*

**Primary Indicator:** Elevated 17-hydroxy-progesterone (17-OHP).

**Symptoms:** Abnormal electrolytes: low sodium, elevated potassium, hypoglycemia, dehydration, cardiac arrhythmia, death, ambiguous genitalia in females. Progressive virilization in both sexes.

**Treatment:** Replace cortisol and aldosterone. Salt supplementation in some cases, surgical correction for females.

## **Congenital Hypothyroidism 1:3,000 - 4,000**

*Absent, hypoplastic, or dysfunctional thyroid gland. About 20% are genetic in origin.*

**Primary Indicator:** Low or normal thyroxine (T4) with elevated thyroid stimulating hormone (TSH).

**Symptoms:** Prolonged neonatal jaundice, poor muscle tone, constipation, lethargy, feeding problems, large tongue, dry and mottled skin, distended abdomen, umbilical hernia.

**Treatment:** Thyroid hormone replacement (L-Thyroxine).

# HEMOGLOBINOPATHY DISORDERS

## **Hemoglobinopathies: Sickle Cell Anemia (HbSS or HbSB<sup>o</sup> Thalassemia). Hemoglobin SC Disease (HbSC) 1:1,300 (GA)\***

*Abnormal hemoglobin production.*

**Primary Indicator:** Abnormal hemoglobin phenotypes.

**Symptoms:** Hemolytic anemia, strokes, splenic sequestration, recurrent pain episodes, acute chest syndrome. Life-threatening infections, hand-foot syndrome, tissue infarction/organ damage and failure.

**Treatment:** Prophylactic penicillin, Hydroxyurea, immunizations, transfusions.

## **Sickle Cell Carrier/Trait**

*Abnormal hemoglobin production.*

**Primary Indicator:** Heterozygous for the sickle cell mutation (Hb S).

**Symptoms:** Sickle cell trait in Athletes can cause significant physical distress during intense exercise, collapse and even death. Muscle pain, abnormal weakness, fatigue, breathlessness.

**Treatment:** Preventative intervention measures include: adequate hydration, frequent rest periods.

*\* Affects one out of every 375 African American infants. This number does not reflect all other groups that are commonly known to have SCD in the U.S.*

## OTHER NBS BLOOD DISORDERS

### **Biotinidase Deficiency 1:60,000**

*Enzyme deficiency, unable to recycle or produce free biotin.*

**Primary Indicator:** Absent or decreased biotinidase enzyme activity.

**Symptoms:** Seizures, hypotonia, apnea, skin rash/infection. Developmental delay, alopecia, deafness, blindness, metabolic acidosis, coma, death.

**Treatment:** Pharmacological doses of oral biotin (5-20 mg/day).

### **Cystic Fibrosis (CF) 1:3,400**

*Defect in the Cystic Fibrosis Transporter Regulator (CFTR) protein.*

**Primary Indicator:** Elevated Immunoreactive Trypsinogen (IRT) and 1 or 2 CFTR mutations.

**Symptoms:** Pulmonary obstruction and exocrine pancreatic dysfunction. Failure to thrive.

**Treatment:** Chest percussion, antibiotics, pancreatic enzyme replacement, proper nutrition and psychosocial support.



## OTHER NBS BLOOD DISORDERS

### **Galactosemia 1:30,000 to 60,000**

*Deficiency of Galactose-1-Phosphate Uridyl Transferase (GALT), unable to convert galactose to glucose. Many variant forms exist.*

**Primary Indicator:** Absent or reduced GALT enzyme activity. Elevated total galactose metabolites.

**Symptoms:** Neonatal jaundice, vomiting, lethargy, diarrhea liver damage. Death from E. coli, sepsis, cataracts, developmental delay, hepatomegaly, Fanconi's syndrome, poor growth.

**Treatment:** Eliminate galactose and lactose from the diet. Soy formulas in infancy. Lactose and galactose free solid foods and medications.

### **Severe Combined Immunodeficiency (SCID) 1:40-75,000 live births**

*Deficiency or body produces non-working T and B-cells.*

**Primary Indicator:** Quantifying T cell receptor excision circles (TRECs). Low TREC level results on NBS dried blood card testing.

**Symptoms:** High number of infections. Infections do not improve with antibiotic treatment for two or more months. Diarrhea, poor weight gain or growth (failure to thrive). Thrush in the mouth or throat that does not go away.

**Treatment:** Bone marrow transplantation. Immunoglobulin replacement therapy.

## OTHER NBS BLOOD DISORDERS

### **Spinal Muscular Atrophy (SMA) 1:12,000**

*Progressive loss of motor neurons. There are 4 primary forms of SMA.*

**Primary Indicator:** Decreased or undetected levels of survival motor neuron 1 (SMN1).

**Symptoms:** Signs and symptoms often appear within the first six months of life. Severe muscle weakness, poor muscle tone, significant developmental delay. Breathing problems, difficulty swallowing, joint abnormalities, inability to stand or walk independently.

**Treatment:** Intrathecal injection of nusinersen. Gene therapy. Supportive therapies: physical, occupational. Respiratory and nutritional therapies. Palliative care for pain, stress and fatigue.

### **X-Linked Adrenoleukodystrophy (X-ALD) 1:17,000**

*Mutations in the ABCD1 gene, which is involved with transport of very long-chain fatty acids into peroxisomes.*

**Primary Indicator:** Elevated C26:0-LPC /C24:0-LPC.

**Symptoms:** Adrenal insufficiency, behavior/learning problems, vision problems, hearing loss, difficulty swallowing, seizures, changes in muscle tone/spasticity, paralysis, coma.

**Treatment:** Treatment for adrenal insufficiency. MRI surveillance for presence or signs of signs of de-myelination. Allogeneic hematopoietic cell transplantation (HCT) or stem cell transplantation. Lorenzo's oil, gene therapy.

# POINT-OF-CARE SCREENING DISORDERS

## **Critical Congenital Heart Disease (CCHD) 2:1,000 births yearly**

*CCHD can result from 14 cardiac lesions. Through pulse oximetry screening, 7 CCHD lesions are commonly identified: Hypoplastic left heart syndrome, pulmonary atresia, Tetralogy of Fallot, total anomalous pulmonary venous return, transposition of the great arteries, tricuspid atresia, truncus arteriosus.*

**Primary Indicator:** Positive pulse oximetry screening, Echocardiogram (ECHO).

**Symptoms:** Cyanosis, tachypnea, dyspnea, edema, puffiness in the face, hands, feet legs or around eyes. Tires easily during feeding, sweating around head, especially during feeding, poor weight gain.

**Treatment:** Catheter procedures to repair simple lesions. Surgical correction of lesions, medications.

## **Hearing Loss 2-3:1,000 live births.**

*Abnormality usually in inner ears.*

**Primary Indicator:** Failure to pass automated screenings of auditory function: Automated Auditory Brainstem Response (A-ABR); or Automated Otoacoustic Emissions (A-OAE).

**Symptoms:** Hearing Impairment and delayed development in verbal expressive language. Relying on symptoms to cue to a diagnostic assessment can lead to a child typically much too old (6 months) to thrive communicatively.

**Treatment:** Multiple. Regardless of whether “treatment” is sign language or hearing aids or surgery, the person’s communicative functioning is better when auditory physiologic screening is complete by 1 month of age, when auditory diagnostic assessment is completed by 3 months of age (for those infants not passing the screening), and when habilitation is initiated by 6 months of age (for those identified with a hearing impairment).



[dph.georgia.gov/NBS](https://dph.georgia.gov/NBS)

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