VIRGINIA DEPARTMENT OF HEALTH

Virginia Newborn Screening Services

Healthcare Practitioner Manual
This project was funded in part by the Maternal and Child Health Bureau (Title V, Social Security Act), Health Resources and Services Administration, U.S. Department of Health and Human Services, administered by the Virginia Department of Health.
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Section 1.
General Information
Introduction

Permanent disability and mental retardation are serious long-term public health, social, and economic problems. However, the disability and retardation caused by an inherited metabolic disorder can sometimes be treated soon after birth. The Virginia General Assembly enacted a law that assigned to the Virginia Department of Health the responsibility of promulgating and enforcing rules and regulations requiring that every newborn be tested for certain genetic disorders. In 1966, legislation was enacted that mandated the screening of all babies for phenylketonuria (PKU). In 1984, the mandate was expanded to include congenital hypothyroidism, maple syrup urine disease, homocystinuria, and galactosemia; in 1986, biotinidase deficiency; in 1989, hemoglobinopathy screening; in 2002, congenital adrenal hyperplasia; and in 2004, with the addition of tandem mass spectrometry (MS/MS) technology, Medium Chain Acyl Co-A Dehydrogenase Deficiency (MCADD) was added to the screening panel. In 2005, legislation was amended to ensure that the Virginia newborn screening panel is consistent with the panel of disorders recommended by the American College of Medical Genetics in its report Newborn Screening: Toward a Uniform Screening Panel and System.

Over 100,000 births are recorded in Virginia each year. The Division of Consolidated Laboratories of the Virginia Department of General Services performs more that a million newborn screening tests per year, including initial and repeat tests. The Division of Child and Adolescent Health of the Virginia Department of Health provides the follow-up services required for greater than 20,000 infants each year. Since the inception of newborn screening, more than 2,000 infants have been clinically diagnosed with one of these disorders.

The success of Virginia Newborn Screening Services depends on the continued collaboration among program staff, physicians, hospitals, and local public health personnel. Efficient, timely collection and rapid flow of specimens to the laboratory, precise analysis, accurate data entry and prompt reporting of results with patient retrieval, and evaluation and retesting are important components of these screening services. When the results of a screening test are questionable, it must be followed by more definitive tests before a diagnosis can be made. In all cases, the infant’s physician is notified and it is his/her responsibility to transmit the information to the family.

Newborn screening nurses in the Division of Child and Adolescent Health of the Virginia Department of Health review all abnormal screening reports, initiate appropriate follow up and compile data concerning suspect and/or confirmed cases. This information is maintained for statistical purposes and is kept confidential.

Prevention of retardation, other developmental disabilities, and the occurrence of infant death are the most important benefits of newborn screening. The second most important benefit is the reduction of expenditures for costly health care for individuals who would have had significant physical and disabilities.

With the addition of the expanded panel disorders, Virginia now screens for a total of 28 disorders. This manual includes general program information and resources, as well as fact sheets for each disorder.
General Information

Virginia Genetics Program

The Virginia Genetics Program is part of a statewide system to reduce unnecessary morbidity from potential or existing genetic conditions by assuring access to the appropriate education, testing, counseling, and treatment to residents of the Commonwealth. Organizationally, the Program is located within the Virginia Department of Health, Division of Child and Adolescent Health, Pediatric Screening and Genetic Services. Virginia Newborn Screening Services is a component of the Virginia Genetics Program.

Virginia Newborn Screening Services

Virginia Newborn Screening Services is a coordinated and comprehensive system consisting of education, dried-blood-spot screening tests, follow up and referral, diagnosis, medical and dietary management, and treatment. The Division of Consolidated Laboratory Services, Virginia Department of General Services, conducts the newborn dried-blood-spot screening tests in collaboration with the Virginia Department of Health.

Newborn screening nurses coordinate follow-up activities until the infant is diagnosed, screened negative, or reaches 6 months of age. Staff members administer the special metabolic formula distribution and modified low-protein food reimbursement services. Regional metabolic treatment centers provide expert consultation on abnormal results, diagnostic testing, and medical and dietary management.

Legislation

Chapter 721 of the 2005 Acts of the General Assembly expands the core panel of conditions identified through newborn dried blood spot screening tests from 11 to 28 conditions, effective March 1, 2006. The legislation is available online at http://leg1.state.va.us/cgi-bin/legp504.exe?051+ful+CHAP0721.

The expanded panel is consistent with the newborn screening uniform condition panel recommended by the American College of Medical Genetics (ACMG) in its report entitled Newborn Screening: Toward a Uniform Screening Panel and System, which was produced for the United States Department of Health and Human Services. The ACMG report is available online at http://mchb.hrsa.gov/screening/.

Resource Materials

The next pages include the following resource materials:

- **List of Newborn Screening Disorders.** Presents a list of heritable disorders and genetic diseases that are required to be identified through newborn dried-blood-spot screening tests.
- **Abnormal Screen Timeline.** Presents a flow chart of newborn screening follow-up activities.
- **Notification of Parental Refusal of Dried-Blood-Spot Screening.** This form can be used to communicate to the Virginia Department of Health that an infant’s parent or legal guardian refuses to consent to the collection and submission of a newborn dried-blood-spot screening specimen because the test conflicts with his/her religious practices or tenets.
- **HIPAA Letter.** This letter is to those healthcare providers who are required by the Code of Virginia to cause the initial collection and submission of a newborn blood-spot screening specimen for testing.
Core Panel of Disorders

Effective March 1, 2006, the Code of Virginia requires that infants under 6 months of age who are born in Virginia must be screened for the following heritable disorders and genetic diseases, which are identified through newborn dried-blood-spot screening tests.

Note: Italicized disorders screened prior to March 1, 2006.

1. Argininosuccinic acidemia (ASA)
2. Beta-Ketothiolase deficiency (βKT)
3. Biotinidase deficiency (BIOT)
4. Carnitine uptake defect (CUD)
5. Citrullinemia (CIT)
6. Congenital adrenal hyperplasia (CAH)
7. Congenital hypothyroidism (CH)
8. Cystic fibrosis (CF)
9. Galactosemia (GALT);
10. Glutaric acidemia type I (GA I)
11. Hemoglobin Sickle/Beta-thalassemia (Hb S/βTh)
12. Hemoglobin Sickle/C disease (Hb S/C)
13. Homocystinuria (HCY)
14. Isovaleric acidemia (IVA)
15. Long-chain hydroxyacyl-CoA dehydrogenase deficiency (LCHAD)
16. Maple syrup urine disease (MSUD)
17. Medium-chain acyl-CoA dehydrogenase deficiency (MCAD)
18. Methylmalonic acidemia (mutase deficiency) (MUT)
19. Methylmalonic acidemia (Cbl A,B)
20. Multiple carboxylase deficiency (MCD)
21. Phenylketonuria (PKU)
22. Propionic acidemia (PROP);
23. Sickle cell anemia (Hb SS disease) (Hb SS)
24. Tyrosinemia type I (TYR I)
25. Trifunctional protein deficiency (TFP)
26. Very long-chain acyl-CoA dehydrogenase deficiency (VLCAD)
27. 3-hydroxy 3-methyl glutaric aciduria (HMG)
28. 3-Methylcrotonyl-CoA carboxylase deficiency (3MCC)
Abnormal Newborn Screen Timeline

Day of Life

0

1-2

1st

6-8

5-6 days from collection)

7-11

8-16

10-21

15-27

5-6 days from collection)

30

31-120

180

BIRTH

Initial Dried-Blood Spot Specimen Collected by Submitter and Sent to DCLS

Specimen received and processed by DCLS

Report Mailed by DCLS to HCP and Submitter

Criticals Called and Abnormal List Sent by DCLS to VDH Newborn Screening Nurse

Report mailed by DCLS to HCP/Submitter

Submitter contacts HCP

HCP contacts Parents to reschedule test

Baby’s appointment

Dried-Blood Spot Specimen Recollected by Submitter and Sent to DCLS

Specimen received and processed by DCLS

Report Mailed by DCLS to HCP and Submitter

Criticals Called and Abnormal List Sent by DCLS to VDH Newborn Screening Nurse

First Abnormal List Follow Up Initiated by VDH Newborn Screening Nurse

If NO resubmission, follow-up letter mailed.

If resubmission, results monitored.

Daily Abnormal List Follow Up Continued by VDH Newborn Screening Nurse

If resubmission is abnormal, follow-up letter mailed.

If NO resubmission, follow-up letter mailed again.

If resubmission is normal, record closed.

4-Month Abnormal Lists Reviewed and Final Request for Resubmission by VDH Newborn Screening Nurse

CLOSE
Notification of Parental Refusal of Dried-Blood-Spot Screening

Virginia Department of Health
Division of Child and Adolescent Health
Pediatric Screening and Genetic Services
109 Governor Street, 8th floor
Richmond, Virginia 23219

Infant’s Name: ____________________________________________
Infant’s Date of Birth: ______________________________________
Mother’s Name: ____________________________________________
Address: ________________________________________________________________
________________________________________________________________

I, __________________________________, hereby acknowledge that I am the parent or legal guardian of the above named infant. I have been informed of the need for newborn dried-blood-spot screening for all disorders mandated by the Code of Virginia. I have also been informed that these disorders could result in mental retardation, physical dysfunction, or even death if unidentified and untreated. I hereby refuse this screening on the grounds that such test conflicts with my religious practices or tenets.

______________________________________  ______________________  
Signature of Parent or Guardian     Date

______________________________________  ______________________  
Signature of Witness Date

Attending Physician’s Name (print): ________________________________________________
Address: _____________________________________________________________________
____________________________________________________________________
Phone: _________________________ Fax: ____________________________________

Please mail to the address above or fax a copy of this document to the Virginia Department of Health, Attention: Newborn Screening Services, Fax (804) 864-7721.

Retain the original for your records.
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Health Insurance Portability and Accountability Act (HIPAA)

To Whom it May Concern:

Virginia Newborn Screening Services (VNSS) is a program of Virginia Department of Health and is conducting the activity described here in its capacity as a public health authority as defined by the Health Insurance Portability and Accountability Act (HIPAA), Standards for Privacy of Individually Identifiable Health Information; Final Rule (Privacy rule) [45 CFR §164.501]. Pursuant to 45 CFR §164.512(b) of the Privacy Rule, covered entities such as your organization may disclose, without individual authorization, protected health information to public health authorities“…authorized by law to collect or receive such information for the purpose of preventing or controlling disease, injury, or disability, including, but not limited to, the reporting of disease, injury, vital events such as birth or death, and the conduct of public health surveillance, public health investigations, and public health interventions…”

VNSS is conducting a public health activity as described by 45 CFR § 164.512(b), and is being authorized by [§32.1-66] of the Code of Virginia. The information being requested represents the minimum necessary to carry out the public health purposes of this project pursuant to 45 CFR §164.514(d) of the Privacy Rule.

If you have questions or concerns please contact:

Kim Barnes
Acting Director of HIPAA Compliance
Virginia Department of Health
109 Governor St. 7th Floor Room 724
Richmond, VA 23219
Phone (804) 864-7661
Section 2.
Metabolic Disorders
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## Description of New Metabolic Disorders

Tables 1. presents an overview of metabolic disorders that have been added to the Virginia Core Panel of Disorders, effective March 1, 2006.

<table>
<thead>
<tr>
<th>Table 1. Organic Acid Disorders (Acylcarnitines)</th>
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<tbody>
<tr>
<td><strong>IVA</strong></td>
</tr>
<tr>
<td>Marker: C5</td>
</tr>
<tr>
<td>Isovaleric Acidemia</td>
</tr>
<tr>
<td>AKA: Isovaleryl CoA Dehydrogenase Deficiency; IVD</td>
</tr>
<tr>
<td>An autosomal recessive disorder. Onset between birth and 1 year of age. It occurs in both acute and chronic forms. <strong>Symptoms</strong> of acute IVA are attacks of vomiting, lack of appetite, and listlessness, lethargy, and severe metabolic keto-acidosis progressing to coma and death. Episodes can be triggered by URI or by excessive consumption of high-protein foods. <strong>Treatment</strong> includes protein-restrictive diet, special dietary formula, and carnitine supplementation.</td>
</tr>
</tbody>
</table>

| **GA-1**                                      |
| Marker: C5-DC                                |
| Glutaric Acidemia Type 1                     |
| AKA; Glutaryl CoA Dehydrogenase Deficiency Type 1; Glutaric Aciduria 1 |
| An autosomal recessive disorder. Onset of symptoms typically 2 and 37 months. **Symptoms** of this enzyme deficiency disorder are characterized by hypoglycemia, dystonia, and dyskinesia. The disorder may appear suddenly and present as vomiting, metabolic acidosis, hypotonia, and central nervous system degeneration. **Treatment** with IV fluids and sodium bicarbonate are used to treat acidosis. Dialysis may be necessary. Dietary restrictions of lysine and tryptophan have had inconsistent outcomes. Carnitine supplementation may be needed. |

| **HMG**                                      |
| Marker: C5-OH                                |
| 3-Hydroxy-3Methylglutaryl-CoA Lyase Deficiency |
| AKA: 3-OH 3-CH3 Glutaric Aciduria; HMG CoA Lyase Deficiency |
| An autosomal recessive disorder. If this disorder is untreated, it is likely to result in death during childhood. **Symptoms** may include metabolic acidosis, hypoglycemia, sensitivity to dietary leucine, carnitine deficiency, hepatomegaly, fever, somnolence, and coma. **Treatment** involves restriction of leucine, supplementary glucose to prevent hypoglycemia, and carnitine supplementation. |

| **MCD /MCCD**                                |
| Marker: C3                                    |
| Multiple CoA Carboxylase Deficiency           |
| AKA: Holocarboxylase Deficiency; Holocarboxylase Synthetase Deficiency |
| An autosomal recessive disorder. A deficiency of biotin, part of the Vitamin B complex, leading to multiple carboxylase deficiency. Incidence is 1 in 87,000. **Symptoms** include seizures, hypotonia, immune system impairment, skin rashes, hair loss, hearing loss, and mental retardation. |
Treatment is oral biotin supplementation, which should be begun immediately upon diagnosis.

| MUT MMA – Methylmalonic Aciduria (Parent disorder) | Methylmalonyl-CoA Mutase (2 types) | An autosomal recessive disorder that causes an enzymatic defect in the oxidation of amino acids is the cause of these conditions, with an incidence of 1 in 50,000 to 1 in 100,000 live births. During the first week of life, 80% become ill, and 90% present by the end of the first month of life. **Symptoms** include lethargy, failure to thrive, vomiting, dehydration, respiratory distress, hypotonia, and hepatomegaly. Acute episodes may include drowsiness, coma, and seizures, with subsequent developmental delays. **Treatment** includes a carefully controlled diet including a low-protein regimen and/or restriction of isoleucine, valine, and threonine. Medical food supplementation may be needed, as may carnitine. |
| Marker: C4-DC | Deficiency 0- accounts for 2/3 of the mutase patients | |
| | Deficiency + | |
| cbl A & cbl B MMA- Methylmalonic Aciduria (Parent disorder) | Adenosyl-Cobalamin Synthesis Defects AKA: Vitamin B12-Responsive, Due to Defect in Synthesis of Adenosylcobalamine | An autosomal recessive disorder may present in the first week of life to completely asymptomatic. **Symptoms** include episodic ketoacidosis accompanied by lethargy and coma that can lead to death. Survivors experience developmental and growth retardation, spastic quadripareisis, dystonia, and seizures. **Treatment** includes a diet restricted in protein and OH-cb1 injections. Carnitine may be useful as well. Cb1A patients have the best prognosis because the biochemical and clinical abnormalities reverse in about 90% of patients when they are provided the hydroxy-cobalamine (OH-cb1) injections. Cb1B-affected patient’s prognosis ranges from alive and well to deceased. |
| Marker: C4-DC | | |
| 3MCC | 3-Methylcrotonyl-CoA Carboxylase Deficiency AKA: 3-Methylcrotonylglycinuria, Isolated Biotin-resistant MCC deficiency, Isolated MCC deficiency, 3-MCC deficiency | An autosomal recessive disorder with presentation generally after 3 months of age. **Symptoms** may include hypoletotic hypoglycemia, metabolic acidosis, hypotonia, muscle atrophy, seizures, dermatological changes, and liver dysfunction with fulminate liver failure and death in some cases. Others present with failure to thrive in conjunction with recurrent episodes of vomiting and diarrhea. In general, the earlier the presentation, the poorer the prognosis. **Treatments** include dietary restrictions of |
| Marker: C5-OH | | |
leucine, with supplementation of glycine and carnitine and/or biotin may be valuable.

| Marker: C3/C2 | Propionic Acidemia  
AKA: Hyperglycinemia with Ketoacidosis, Lactic Acidosis, Propionic Type, Ketotic Glycinemia, PCC Deficiency, Propionyl CoA Carboxylase Deficiency; Methylmalonic Acidemia | An autosomal recessive disorder. This disorder usually results in catastrophic illness beginning in the newborn period. Incidence is 1 in 100,000 live births. Primary symptoms include protein intolerance, vomiting, failure to thrive, lethargy, and profound metabolic acidosis. Brain damage, including coma and generalized seizures, and death result if not treated. **Treatment** includes protein restriction and often calls for supplementation by medical foods. Fluids and electrolyte therapy may be needed. Acidosis is resolved by sodium bicarbonate or by dialysis. Secondary carnitine deficiency is likely to occur, requiring supplementation. |
| BKT | Mitochondrial Acetoacetyl-Co A Thiolase  
AKA: 3-Ketothiolase Deficiency  
Beta-Ketothiolase Deficiency | An autosomal recessive disorder. Age range at onset is between 3 days and 48 months of age. The main symptom of this disorder is recurrent, severe metabolic acidosis. Sodium bicarbonate and intravenous fluids are the usual treatment for acidosis; dialysis may be needed. Carnitine supplementation has been helpful in some cases. |
| VLCAD / VLCADD | Very Long-Chain Acyl-CoA Dehydrogenase Deficiency | A rare autosomal recessive condition in which the body cannot oxidize fatty acids because an enzyme is either missing or not functioning correctly. Initial symptoms may include hypoketotic hypoglycemia, hepatocellular disease, and cardiomyopathy; fatal infantile encephalopathy may be the only indication of the condition. **Treatment** consists of avoidance of fasting and use of IV glucose when food cannot be tolerated. Intake of long-chain fatty acids should be avoided. Supplemental carnitine is recommended for some affected children. |
| LCHAD / LCHADD | Long-Chain Hydroxyacyl-CoA Dehydrogenase Deficiency  
AKA: Long-chain L-3-OH acyl-CoA dehydrogenase deficiency | A rare autosomal recessive condition in which the body cannot oxidize fatty acids because an enzyme is either missing or not functioning correctly. Typical symptoms are hypoglycemia, lethargy, failure to thrive, and developmental delay, often accompanied by... |
hypotonia, hepatic dysfunction, and cardiomyopathy. Sudden infant death may occur. **Treatment** consists of avoidance of fasting, a high-carbohydrate, low-fat diet supplemented with MCT (medium-chain triglyceride) oil.

**TFP**

Trifunctional Protein Deficiency

A rare autosomal recessive condition that tends to mimic LCHAD. Individuals are unable to break down long-chain fatty acids into an energy source. **Symptoms** include metabolic crisis, which can occur during periods of fasting and can cause episodes of hypoglycemia, vomiting, coma, and death. Severe, untreated cases may present as SIDS. **Treatment** is the same as LCHAD.

**CUD**

Carnitine Uptake /Transporter Defect

A rare autosomal recessive condition that results from the body’s inability to transport carnitine into cells. Onset of symptoms may occur in infancy or childhood. **Symptoms** include hypoketotic hypoglycemia, seizures, vomiting, and lethargy progressing to coma. **Treatment** is carnitine supplementation and no fasting.

<table>
<thead>
<tr>
<th>Marker: C16-OH</th>
<th>Marker: C16-OH</th>
<th>Marker: C0</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TYR 1</strong></td>
<td>Tyrosinemia Type 1 AKA: Hepatoren tyrosinemia</td>
<td>An autosomal recessive amino acid disorder caused by the person’s inability to completely metabolize the amino acid tyrosine (a deficiency in the fumaryl acetoacetate hydrolase enzyme activity) causing the build up of tyrosine in the blood. <strong>Symptoms</strong> typically manifests within the first year of life with dysfunction of the liver, kidneys, and nerves, resulting in irritability, rickets, or even liver failure and death. <strong>Treatment</strong> is dietary restriction of phenylalanine, methionine, tyrosine, and administration of the drug nitisinone, brand name Orfadin. This treatment regime is successful in delaying the clinical symptoms of tyrosinemia; the only effective long-term treatment is liver transplantation.</td>
</tr>
<tr>
<td>Marker: Tyrosine</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ASA</strong></td>
<td>Argininosuccinic Aciduria (Acidemia) (Urea cycle disorder)</td>
<td>A rare autosomal recessive condition. <strong>Symptoms</strong>: Neonatal onset presents in the first 2-3 days of life with vomiting, lethargy, respiratory alkalosis, and hypothermia progressing to encephalopathy, cerebral</td>
</tr>
</tbody>
</table>
| Marker: Citrulline | Citrulinenemia  
AKA: Arginosuccinic Acid Synthetase Deficiency, ASS Deficiency, Urea Cycle, Disorder, Citrullinemia Type, Citrullinuria | An autosomal recessive disorder caused by a deficiency in the argininosuccinate synthetase enzyme activity causing the build up of the amino acid citrulline and ammonia in the blood. Clinical symptoms include lack of appetite, vomiting, listlessness, seizures, and coma. **Treatment** includes a high-calorie and protein-restricted diet, arginine supplementation, and administration of sodium benzoate and sodium phenylacetate. Dialysis may be necessary in some affected individuals. |
| --- | --- | --- |

| CF  
Marker: IRT | Cystic Fibrosis | An autosomal recessive disorder characterized by pulmonary obstruction and/or exocrine pancreatic dysfunction. The major and most severe genetic mutation causing CF is a three-based pair deletion (F508) in the cystic fibrosis transmembrane regulator (CFTR) gene with a resulting increase in the pancreatic enzyme immunoreactive trypsinogen. |
| --- | --- | --- |
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Key Points for Healthcare Providers
Working With Parents of a Child With a Metabolic Disorder

If a Child in Your Practice is Suspected of Having a Metabolic Disorder:
1. Make sure you have contact with the Metabolic Treatment Center in your area. Staff there will provide you with information as to what to do next. They will contact you when a child is identified as highly probable for a metabolic disease.
2. Avoid overly alarming the child’s parents if the diagnosis has not been confirmed.
3. The child will need additional testing or diagnostic evaluation. Make certain that the parents understand the importance of following the recommendations for additional testing and referral.

Follow Up After Confirmation of Diagnosis:
1. Parents should understand that treatment is life-long and that compliance with dietary or medication management is imperative to the child’s health, growth, and development.
2. Infants and children with a metabolic disorder should have regular follow-up appointments with a metabolic disease specialist.
3. Parents should be educated that if the infant/child shows symptoms of illness—such as vomiting, lethargy or lack of appetite—they should seek immediate medical attention.
4. Long-term management, including compliance with treatment recommendations, is essential to the child’s well being. A multidisciplinary approach that includes the following specialties is recommended: pediatrics, genetics, and nutrition. Parents should understand that treatment is not curative and all morbidity cannot necessarily be prevented.
5. Genetic counseling services are recommended. Information about these services can be obtained from the Metabolic Treatment Center.
6. Inform the parents that Virginia Newborn Screening Services will refer the child to Care Connection for Children (CCC), which is a statewide network of Centers of Excellence for children with special health care needs that assists families in accessing health care services through care coordination, family-to-family support, medical insurance benefit coordination, and community resources. CCC is sponsored by the Virginia Department of Health, Division of Child and Adolescent Health, Children with Special Health Care Needs Program.
7. For more information about newborn screening in general and about specific disorders, contact the National Newborn Screening and Genetics Resource Center, 1912 W. Anderson Lane, Suite 210, Austin, TX 78757; Web site http://genes-r-us.uthscsa.edu.
Metabolic Medical Consultants

Three regional metabolic treatment centers are available for children identified through Virginia Newborn Screening Services. Each center is available to provide metabolic consultation to healthcare providers. The consultants are listed below.

Northern & Central Regions

Arti Pandya, M.D.
Assistant Professor Human Genetics
Virginia Commonwealth University
MCV Campus
1101 E. Marshall St.
PO Box 980033
Richmond, VA 23298-0033
(804) 828-9632 ext. 139
(804) 828-0951 Pager# 3801
Nutritionist: Laura Duncan, M.S., R.D.

Western & Southwestern Regions

William Wilson, M.D.
Professor of Pediatrics
Department of Pediatrics
University of Virginia Health Systems
Box 800386 UVA Health Systems
Charlottesville, VA 22908-0386
(434) 924-2665
(434) 971-6040 Pager
Nutritionist: Barbara Gooding, R.D.

Hampton Roads & Eastern Shore

Virginia Proud, M.D.
Director, Division of Medical Genetics
Children’s Hospital of The King’s Daughters
601 Children’s Lane
Norfolk, VA 23507-1921
(757) 668-9723
Nutritionist: To be determined.
Fact Sheets: Metabolic Disorders

The following fact sheets are intended to provide healthcare providers with an overview of all metabolic disorders that will be included in the core panel of disorders, effective March 1, 2006. The fact sheets are organized under four categories: (1) Amino Acid Disorders, (2) Fatty Acid Oxidation Disorder, (3) Organic Acid Disorders (Acylcarnitines), and (4) Other Disorders.

Amino Acid Disorders
- Argininosuccinic Aciduria (Urea Cycle Disorder)
- Citrullinemia (Urea Cycle Disorder)
- Homocystinuria
- Maple Syrup Urine Disease
- Phenylketonuria (PKU)
- Tyrosinemia Type I

Fatty Acid Oxidation Disorders (Acylcarnitines)
- Carnitine Uptake/Transport Defect
- Long-Chain Hydroxyacyl-CoA Dehydrogenase Deficiency
- Very Long-Chain Acyl-CoA Dehydrogenase Deficiency
- Trifunctional Protein Deficiency

Organic Acid Disorders (Acylcarnitines)
- Adenosyl-Cobalamin Synthesis Defects (cbl A&B)
- Beta-Ketothiolase Deficiency (BKT)
- Glutaric Acidemia Type I (GAI)
- 3-Hydroxy-3Methylglutaryl-CoA Lyase Deficiency (HMG)
- Isovaleric Acidemia (IVA)
- 3-Methylcrotonyl-CoA Carboxylase Deficiency (3MCC)
- Methylmalonyl-CoA Mutase Deficiency (MUT)
- Multiple CoA Carboxylase Deficiency (MCD)
- Propionic Acidemia (PPA)

Other Metabolic Disorders
- Biotinidase Deficiency
- Galactosemia
Amino acidemias are inherited conditions that affect the way a person’s body uses a part of food called amino acids. A person with an amino acidemia cannot break down a specific amino acid from food. Amino acids are needed for proper growth and development, but too much can cause serious health problems. In the case of an amino acidemia, a specific amino acid(s) builds up in the blood and may penetrate and damage the brain and other organs of the body. The high levels of amino acid(s) ultimately cause serious health problems.\(^1\)

- Argininosuccinic Aciduria (ASA)
- Citrullinemia (CIT)
- Homocystinuria
- Maple Syrup Urine Disease
- Phenylketonuria (PKU)
- Tyrosinemia Type I

Description:
Argininosuccinic Aciduria (ASA) is one of the urea cycle disorders and is caused by the deficiency of the enzyme argininosuccinic acid lyase. It is an autosomal recessive condition. This deficiency prevents the conversion of argininosuccinic acid into arginine. Individuals with ASA also cannot convert waste nitrogen, in the form of ammonia, into urea. This causes the ammonia to build up in the person’s blood. Hyperammonemia is especially toxic to the nervous system and can result in brain damage. Occasionally, an individual may inherit a milder form of the disorder in which ammonia accumulates in the bloodstream only during periods of illness or other stress.

Symptoms:
There are two clinical forms of ASA: neonatal and sub-acute or late forms. Symptoms of the neonatal form are severe hyperammonemia accompanied by lack of appetite, tachypnea, persistent vomiting, listlessness, seizures, coma, and hepatomegaly. Clinical features typically present 24 to 72 hours after the first protein feeding. There is a high mortality rate. Late-onset patients may present with developmental delay or non-specific mental retardation, and/or skin and hair abnormalities between a few months and years of age.

Incidence in General Population:
1:70,000 live births

Diagnosis:
Newborn screening—Tandem mass spectrometry (MS/MS) identifies (secondary) elevations in the amino acid citrulline. A second dried-blood-spot filter paper card may be requested by the Newborn Screening Laboratory if the initial screening result is above the normal range. Infants with presumptive positive screening (critical) results require prompt follow up. If this occurred, the clinician would be contacted by the Metabolic Treatment Center. When notified of these results, the clinician should immediately check on the clinical status of the baby and facilitate referral to the Metabolic Treatment Center. The Metabolic Treatment Center will provide consultation and assistance with diagnostic testing.

Situations That Risk Metabolic Decompensation:
General anesthesia should be used with caution in patients with this condition as it can cause hyperammonia.

Monitoring:
- Clinical observation is an important tool for monitoring patients with ASA. It is important for primary care provider and the Metabolic Treatment Center to develop an ongoing collaborative relationship in caring for these patients.
- Carefully assess infants presenting with unexplained vomiting, lethargy, rapid respirations with respiratory alkalosis, and hypothermia.
- Late onset patients may present with developmental delay, non-specific mental retardation, seizures, hepatomegaly, and/or skin and hair abnormalities, between a few months and years of age.
Treatment:
- Treatment may include a high-caloric, protein-restrictive diet, arginine supplementation to help complete the urea cycle, essential amino acid supplementation, ammonia scavenging drugs in some cases, and supplemental carnitine if patient has a secondary deficiency.
- Liver transplantation offers a partial correction of the enzyme deficiency and improved metabolic status.
- Patients must avoid fasting; during stressors, such as illness, they need to supplement with high carbohydrates, non-protein calories to avoid catabolism.
- When left untreated, brain damage, coma, and death will occur.
- Patients who survive the severe hyperammonemia episodes usually have mental retardation and neurological dysfunction.

Illness:
- Patients with ASA must be monitored closely during times of illness, especially infections. Stressors, such as fever, can cause the body to break down its own proteins and exceed the capacity of the abnormal urea cycle to dispose of the waste nitrogen by-products.
- A sick-day plan should be formulated with the Metabolic Treatment Center.
- During illness, it is recommended that the protein intake be further restricted or stopped and consumption of high carbohydrate drinks is advised in order to maintain hydration. The patient should be seen by his/her physician. (However, prolonged fasting can result in catabolism.)
- Should hospitalization be necessary, treatment may consist of medications that help the body dispose of nitrogen-containing wastes. Hemodialysis may be required to help rid the body of excess ammonia during extreme illness and severe hyperammonemia.
- Consult with the Metabolic Treatment Center within 24 hours of the onset of an illness or at the time of hospitalization.

Immunization:
Immunizations must be kept current.

Surgical/Surgical Procedures:
Major stresses, such as surgery or accidents, can be complicated for ASA patients. Extreme care is required to avoid problems during such periods.

Growth and Development:
- It is crucial to closely monitor ASA patients. Despite optimum treatment, they are prone to periodic bouts of hyperammonemia, which can be life threatening and damaging.
- There is a direct correlation between the length of time a patient is in hyperammonemic coma as a neonate and the neurologic complications, including mental retardation. While early diagnosis and treatment may be lifesaving, neurologic damage is not usually prevented.
- In some patients, chronic hepatic dysfunction results in cirrhosis and liver failure, and a liver transplant may be indicated despite adequate treatment and metabolic control.
FACT SHEET
Healthcare Provider

Citrullinemia (CIT)
Citrullinemia Type I

Description:
Citrullinemia is a rare autosomal recessive disorder caused by a missing or poorly functioning enzyme, argininosuccinate synthetase (ASS) enzyme activity. Argininosuccinate synthetase is one of six enzymes that play a role in the breakdown and removal of waste nitrogen from the body, a process known as the urea cycle. The lack of this enzyme results in excessive accumulation of citrulline and nitrogen, in the form of ammonia (hyperammonemia), in the blood.

Symptoms:
Most patients present with symptoms early in the neonatal period but there may be later onset. Infants are generally well for the first 24-72 hours but then may demonstrate lethargy, poor feeding, vomiting, grunting respirations, tachypnea, hypothermia, progressing to opisthotonus, seizures, cerebral edema, coma, apnea, and death if not treated. Infants with the severe form who are treated promptly may survive for an indeterminate period of time but may have neurological deficit. Milder variants, asymptomatic individuals and intra-family variability have been reported.

Incidence in General Population:
1:57,000 live births worldwide

Diagnosis:
Newborn screening—Tandem mass spectrometry:
- Citrulline—very elevated.
- Arginine—low/undetectable.
A second dried-blood-spot filter paper card may be requested by the Newborn Screening Laboratory if the initial screening result is above the normal range. Infants with presumptive positive screening (critical) results require prompt follow up. If this occurred, the clinician would be contacted by the Metabolic Treatment Center. When notified of these results, the clinician should immediately check on the clinical status of the baby and facilitate referral to the Metabolic Treatment Center. The Metabolic Treatment Center will provide consultation and assistance with diagnostic testing.

Monitoring:
- When informed of an infant with a presumptive positive screening test result, the clinician should immediately check on the clinical status of the baby and facilitate referral to a metabolic consultant.
- Metabolic Treatment Center will provide the appropriate monitoring and follow up of a patient with Citrullinemia.
- It is important for the primary care provider and the Metabolic Treatment Center staff to develop an ongoing collaborative relationship in caring for these patients.

Treatment:
Rescue of an infant from hyperammonemic encephalopathy may be possible with aggressive hemodialysis and specialized care. Maintenance treatment consists of a protein-restricted diet, ammonia disposal drugs, arginine supplementation, and aggressive intervention for recurrent bouts of hyperammonemia. Infants with severe hyperammonemia require prompt treatment, which may include hemodialysis or the use of intravenous medications that help reduce the ammonia level. Liver transplantation is an effective treatment. Lifelong dietary management is necessary and requires the services of a metabolic nutritionist.
Illness:
- Patients with Citrullinemia must be monitored closely during times of illness.
- Infectious diseases, such as colds and flu, can be very serious and even life threatening in these children.
- A sick-day plan should be formulated with the Metabolic Treatment Center.
- During illness, it is recommended that dietary protein be further reduced or eliminated and consumption of high carbohydrate drinks is advised in order to maintain hydration. The patient will need to be seen by his/her physician.
- Should hospitalization be necessary, treatment may consist of medications that help the body dispose of waste nitrogen. Hemodialysis may be required to help rid the body of excess ammonia during episodes of severe hyperammonemia.
- Consult with the Metabolic Treatment Center within 24 hours of the onset of an illness or at the time of hospitalization.

Immunizations:
Immunizations must be kept current.

Surgical/Surgical Procedures:
Major stresses, such as surgery or accidents, can be complicated for these patients. Extreme care is required to avoid problems during such periods.

Growth and Development:
- It is crucial to closely monitor citrullinemia patients. Despite optimum treatment, they are prone to periodic bouts of hyperammonemia, which can be life threatening and damaging.
- There is a direct correlation between the length of time a patient is in hyperammonemic coma and IQ. While early diagnosis and treatment may be lifesaving, neurologic damage is not usually prevented.
- In some patients, chronic hepatic dysfunction results in cirrhosis and liver failure, and a liver transplant may be indicated despite adequate treatment and metabolic control.

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November 2005
FACT SHEET
Healthcare Provider

Homocystinuria

Description:
Homocystinuria (HCU) is an autosomal recessive disorder caused by a defect in the catabolism of sulfur-containing amino acids. The most common cause of HCU is a deficiency of the enzyme cystathionine B-synthase. Elevated levels of homocysteine, methionine, and metabolites of homocysteine accumulate in the blood and urine of these patients.

Incidence in General Population:
1: 150,000 live births

Symptoms:
Typically the child with HCU is asymptomatic in the first few months of life.

Untreated Clinical Features
- Physical Disabilities: Marfanoid habitus, ectopia lentis, glaucoma, cataracts, osteoporosis with bone deformities, high palatal arch, and muscle weakness with a shuffling gait.
- Developmental Disabilities: Mental retardation, developmental delay is reported in 65% to 80% of untreated individuals.
- Mortality: Frequently due to thromboembolism in cerebral, pulmonary, renal, and myocardial circulation. Death usually occurs within the first year of life. Death can also occur later from thromboembolism.

Symptomatic Diagnosis
A symptomatic diagnosis is limited due to nonspecific features during the newborn period. Ocular abnormalities, because of their distinctive lens displacement, may be the only symptoms leading to an early clinical diagnosis.

Variants:
There are several forms of HCU that are characterized by normal or low blood levels of methionine and the absence of ocular abnormalities. These variants are additional disorders of methionine metabolism, including decreased N5 methyltetrahydrofolate homocysteine methyltransferase activity due to vitamin B12 deficiency and decreased N5, 10-methyl tetrahydrofolate reductase activity.

Diagnosis:
Newborn Screening—Tandem mass spectrometry identifies elevations in blood methionine on dried-blood-spot filter paper. A normal range is 0-61 μmol/l. A second dried-blood-spot filter paper card may be requested by the Newborn Screening Laboratory if the initial screening result is above the normal range. Infants with presumptive positive screening (critical) results require prompt follow up. If this occurred, the clinician would be contacted by the Metabolic Treatment Center. When notified of these results, the clinician should immediately check on the clinical status of the baby and facilitate referral to the Metabolic Treatment Center. The Metabolic Treatment Center will provide consultation and assistance with diagnostic testing.

Monitoring:
Individuals diagnosed with HCU require life-long medical management and dietary therapy coordinated by nutrition and metabolic specialists. Clinical observation is important for healthcare providers caring for patients with Biotinidase. It is important for primary care provider and the Metabolic Center to develop an ongoing collaborative relationship in caring for these patients.
Treatment:
Early diagnosis and treatment is essential for an improved prognosis. Children identified during the newborn period, or even later in infancy, can prevent or greatly reduce the severity of the clinical consequences. Individuals with HCU require a diet restricted in methionine and supplemented with cystine and medication (betaine). Folic acid and B12 supplements may be beneficial for some patients. Anticoagulants may also be indicated but not typically for infants. Some individuals with HCU may respond to vitamin B6 (pyridoxine) supplements.

Illness and Immunizations:
- Immunizations should be kept current.
- Consult with the Metabolic Treatment Center within 24 hours of the onset of an illness or at the time of hospitalization.

Growth and Development:
Monitor the child for normal growth and development.

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FACT SHEET
Healthcare Provider

Maple Syrup Urine Disease

Description:
Maple syrup urine disease (MSUD) is an autosomal recessive metabolic disorder. It is caused by a deficiency in branch-chain ketoacid decarboxylation. The result is high body fluid (serum, urine, and spinal fluid) levels of leucine, isoleucine, valine, and their corresponding ketoacids. MSUD has been diagnosed in people worldwide but is most prevalent in the Mennonite population of Lancaster, Pennsylvania.

Incidence in General Population:
1:100,000 live births

Symptoms:
Affected infants are normal at birth. Within 4 to 5 days, however, symptoms begin to occur.

Untreated Clinical Features
- Physical disabilities: Spastic quadriplegia, dystonic posturing, dysarthria, poor physical growth, seizures, central nervous system depression, coma, severe metabolic acidosis, and hypoglycemia.
- Developmental disabilities: irreversible mental retardation.
- Mortality: Lethal usually within two weeks to one month of life.

Symptomatic Diagnosis
A symptomatic diagnosis is very possible and should be considered in any infant with severe acidosis in the first 10 days of life. Initial symptoms are poor feeding and marked lethargy along with a characteristic odor of the urine.

Variants
There are three variant forms of MSUD: intermediate, intermittent, and thiamine-response forms. All three are associated with deficient decarboxylation of all three branched-chain ketoacids. Physical disabilities range from occasional developmental delay to mental retardation and ataxia.

Diagnosis:
Newborn Screening—Tandem mass spectrometry identifies elevations in blood leucine on dried blood spot filter paper. A normal range is 0-277 µmol/l. A second-dried-blood-spot filter paper card may be requested by the Newborn Screening Laboratory if the initial screening result is above the normal range. Infants with presumptive positive screening (critical) results require prompt follow up. If this occurred, the clinician would be contacted by the Metabolic Treatment Center. When notified of these results, the clinician should immediately check on the clinical status of the baby and facilitate referral to the Metabolic Treatment Center. The Metabolic Treatment Center will provide consultation and assistance with diagnostic testing.

Monitoring:
Individuals diagnosed with MSUD require life-long medical management and dietary therapy coordinated by nutrition and metabolic specialists. Clinical observation is important for healthcare providers caring for patients with MSUD. It is important for primary care provider and the Metabolic Treatment Center to develop an ongoing collaborative relationship in caring for these patients.
Treatment:
- Dietary restriction of branched-chain amino acids and supplemental vitamin B1 (thiamine) is essential for a good prognosis.
- During periods of metabolic decompensation, peritoneal dialysis, and/or treatment with intra-venous hyperalimentation without branched-chain amino acids (leucine, isoleucine, and valine) may be necessary.

Illness and Immunizations:
- Immunizations should be kept current.
- Consult with the Metabolic Treatment Center within 24 hours of the onset of an illness or at the time of hospitalization.

Growth and Development:
Monitor child for normal growth and development.

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November 2005
Phenylketonuria (PKU)

**Description:**
Phenylketonuria is an autosomal recessive disorder resulting from a defective phenylalanine metabolic pathway. The absence or deficiency of enzyme phenylalanine hydroxylase prohibits the conversion of phenylalanine to tyrosine. This causes phenylalanine and its breakdown chemicals to accumulate in the blood and body tissues. In the “classic” form of PKU, the enzyme that breaks down phenylalanine is completely or nearly completely deficient. Hyperphenylalaninemia means an elevation of phenylalanine in the blood. It is sometimes also used to describe a group of other disorders that may be caused by a partial deficiency of the phenylalanine breakdown enzyme or the lack of another enzyme important to the processing of this amino acid.

**Incidence in General Population:**
1:25,000 live births

**Symptoms:**
With early treatment, normal intelligence and development can be expected. Infants with PKU appear normal at birth and for the first few months of life. Patients with undiagnosed PKU have progressive developmental delay in the first year of life, mental retardation ranging from moderate to severe, seizures, abnormal gait, autistic-like behavior, and an unusual “musky” odor to their urine. Some other commonly observed features in untreated children include microcephaly, prominent cheek and upper jawbones with widely spaced teeth, poor development of tooth enamel, and decreased body growth.

**Diagnosis:**
Newborn screening—Tandem mass spectrometry identifies elevations in blood phenylalanine on dried-blood-spot filter paper. A normal range is 0-124 µmol/l. A second dried-blood-spot filter paper card may be requested by the Newborn Screening Laboratory if the initial screening result is above the normal range. Infants with presumptive positive screening (critical) results require prompt follow up. If this occurred, the clinician would be contacted by the Metabolic Treatment Center. When notified of these results, the clinician should immediately check on the clinical status of the baby and facilitate referral to the Metabolic Treatment Center. The Metabolic Treatment Center will provide consultation and assistance with diagnostic testing.

**Monitoring:**
Individuals diagnosed with PKU require life-long medical management and dietary therapy coordinated by nutrition and metabolic specialists. Clinical observation is important for healthcare providers caring for patients with PKU. It is important for primary care provider and the Metabolic Treatment Center to develop an ongoing collaborative relationship in caring for these patients.

**Treatment:**
Some phenylalanine is essential for normal growth and development. The goal of PKU treatment is to provide the essential amino acids and maintain a low blood level of phenylalanine. This requires a diet that restricts the amount of phenylalanine, but provides all of the other essential amino acids. This means that high-protein foods—such as meat, eggs, milk, and cheese—should be avoided. The diet is protein supplemented with phenylalanine-reduced formula. Blood phenylalanine levels are checked frequently and the diet adjusted accordingly to keep the phenylalanine level within the recommended control range for age. Currently this treatment is recommended for life, particularly for individual with “classic” PKU.
**Illness and Immunizations:**
Fever and illness can cause normal body proteins to break down, the liberation of the body’s own amino acids, and ultimately, a rise in the blood phenylalanine level.

**Surgical/Surgical Procedures:**
Discuss any plans for surgical and dental procedures with the Metabolic Treatment Center.

**Growth and development:**
- It is crucial to closely monitor all growth parameters on a regular basis.
- In cases with neurological deficits, the child should be referred to an early intervention program and developmental progress should be closely monitored by both the metabolic team and the primary care provider.

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November 2005
Tyrosinemia Type I

Description:
Tyrosinemia Type I is a rare autosomal recessive disorder due to fumaryl acetoacetase deficiency, an enzyme involved in the catabolism of tyrosine. Tyrosinemia Type I, the most severe form of tyrosinemia, results in the accumulation of tyrosine and its metabolites in the liver causing severe liver damage. In the acute infantile form, onset of symptoms occurs between 2 and 6 weeks of age with symptoms of failure to thrive and severe liver dysfunction.

Symptoms:
Patients with Tyrosinemia Type I may have acute liver disease, episodes of peripheral neuropathy, and chronic liver disease. Kidney function and peripheral nerves also are affected. Effects on the kidneys can range from mild tubular dysfunction to renal failure. Symptoms may include poor weight gain, fever, diarrhea, vomiting, enlarged liver and spleen, swelling of the legs, and increased tendency of bleeding.

Diagnosis:
Newborn screening—Tandem mass spectrometry identifies elevated Tyrosine. Some cases of tyrosinemia may not be detected by newborn screening when specimens are collected in the first few days of life, as tyrosine levels may not be sufficiently elevated for detection by tandem mass spectrometry. A second dried-blood-spot filter paper card may be requested by the Newborn Screening Laboratory if the initial screening result is above the normal range. Infants with presumptive positive screening (critical) results require prompt follow up. If this occurred, the clinician would be contacted by the Metabolic Treatment Center. When notified of these results, the clinician should immediately check on the clinical status of the baby and facilitate referral to the Metabolic Treatment Center. The Metabolic Treatment Center will provide consultation and assistance with diagnostic testing.

Monitoring:
When receiving a presumptive positive result, the clinician should immediately check on the clinical status of the baby and consult with the Metabolic Treatment Center. Long-term management, monitoring, and compliance with treatment recommendations are essential to the child’s well being. Regular monitoring of laboratory values is also part of the treatment. Monitoring includes:
- Regular monitoring of plasma amino acid concentrations.
- Regular clinic appointments (this varies between clinics and depends on patient’s status).

Treatment:
Early diagnosis and prompt treatment is essential for an improved prognosis. There are three strategies for tyrosinemia type I.
- Treatment consists of a special dietary formula restricted in tyrosine and phenylalanine.
- Medication treatment with Nitisinone (Orfadin®) has been successful to date and has improved the outcome in tyrosinemia type I.
- In some cases, liver transplantation has been an effective treatment.

Illness and Immunizations:
During illness, it is important to minimize tissue breakdown. This can be accomplished by encouraging a continuous intake of the specialized metabolic formula during these times. It is important to avoid dehydration. With severe illness, it may be necessary to introduce an intravenous line for fluids or a
nasogastric tube for formula intake. There are no immunization contraindications because of Tyrosinemia.

**Growth and Development:**
- A child with appropriately managed blood tyrosine levels can look and act like other children of the same age.
- It is crucial to closely monitor all growth parameters on a regular basis.
- To support ideal growth for children with tyrosinemia, intakes of energy (calories), protein, carbohydrate, fat, vitamins, and minerals are carefully monitored.

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November 2005
Fatty acid oxidation disorders are inherited conditions that affect the way a person’s body breaks down certain fats (fatty acids). A person with a fatty acid oxidation disorder cannot break down stored fat for energy. Consequently, the body begins to fail once the food the person has eaten runs out. In addition, fatty acids build up in the blood. In the case of fatty acid oxidation disorders, the inability to break down fats for energy and the build up of fatty acids can cause serious health problems.2

- Carnitine Uptake Defect (CUD)
- Long-Chain Hydroxyacyl-Co A Dehydrogenase Deficiency
- Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCADD)
- Trifunctional Protein Deficiency
- Very Long-Chain Acyl-CoA Dehydrogenase Deficiency

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FACT SHEET
Healthcare Provider

Carnitine Uptake Defect (CUD)
Carnitine Transport Defect (CTD)

Description:
Carnitine Uptake Defect is an autosomal recessive disorder in which the body cannot oxidize fatty acids properly. The disorder is caused by a defect in the plasma membrane transport of carnitine. This error results in a deficiency of carnitine, a failure of acylcarnitine formation, and inadequate transport of certain fatty acids into the mitochondria. The mitochondrial β-oxidation pathway plays a major role in energy production, especially during periods of fasting. The ability of the cells to produce energy and to remove toxic wastes is impaired. Carnitine deficiency can be life threatening.

Incidence in General Population:
1:100,000 live births

Symptoms:
Onset of symptoms may occur in two forms: one with onset in infancy, between birth and 30 months of age, and a late onset form between 1 and 7 years of age. Symptoms may include hypoketotic hypoglycemia, cardiomypathy, muscle weakness, seizures, vomiting, liver dysfunction, and lethargy progressing to coma. If left untreated, death can occur.

Diagnosis:
Newborn Screening—Tandem mass spectrometry identifies reduced concentrations of free carnitine (“C0”). A second dried-blood-spot filter paper card may be requested by the Newborn Screening Laboratory if the initial screening result is above the normal range. Infants with presumptive positive screening (critical) results require prompt follow up. If this occurred, the clinician would be contacted by the Metabolic Treatment Center. When notified of these results, the clinician should immediately check on the clinical status of the baby and facilitate referral to the Metabolic Treatment Center. The Metabolic Treatment Center will provide consultation and assistance with diagnostic testing.

Monitoring:
Plasma levels monitored for free carnitine levels.

Treatment:
Treatment consists of L-carnitine supplementation and avoidance of fasting. L-carnitine can reverse the heart problems and muscle weakness. Infants and young children need to eat often to avoid problems. They should go no more than 4 to 6 hours without food. It is important that they be fed during the night. They need to be awakened if they do not wake up on their own.

Illness and Immunizations:
- Patients with CUD must be monitored closely during times of illness. Conditions that can cause metabolic de-compensation include:
  - Poor appetite
  - Low energy or excessive sleepiness
  - Vomiting
  - Diarrhea
  - Infection
  - Fever
  - Persistent muscle pain or weakness
• Infants and children with CUD need to consume extra-starchy food and drink more fluids during any illness—even if they do not feel hungry. Hospitalization may be necessary.
• Immunizations should be kept current.

Surgical/Surgical Procedures:
Major stresses, such as surgery or accidents, can be complicated for a CUD patient. Extreme care is required to avoid problems during such periods.
• Discuss any plans for surgical and dental procedures with the Metabolic Treatment Center.
• Preoperative fasting should be avoided with 10% dextrose being started preoperatively and continuing postoperatively until the child is eating and drinking well.
• If complicated surgery or a postoperative period as an inpatient is required, the procedure should be done at a hospital with a metabolic service.

Growth and Development:
It is crucial to closely monitor all growth parameter on a regular basis.
FACT SHEET  
Healthcare Provider

Long-Chain Hydroxy Acyl-CoA Dehydrogenase Deficiency (LCHADD)

Description:
Long-Chain Hydroxy Acyl-CoA Dehydrogenase Deficiency is an autosomal recessive genetic condition caused by enzyme defects in the mitochondrial beta-oxidation cycle. Individuals with this disorder are unable to break down fatty acids into an energy source. Metabolic crisis can occur during periods of fasting and can cause episodes of hypoglycemia, vomiting, coma, and even death.

Incidence in General Population:
1:75,000 live births

Symptoms:
Metabolic crisis may be precipitated by intercurrent illnesses and may present with symptoms that include hypoglycemia, lethargy, failure to thrive, hypotonia, seizures, developmental delay, peripheral neuropathy, cardiomyopathy, coma, or sudden death. Severe, untreated cases may present as SIDS. Affected infants and children usually present by 2 years of age.

Diagnosis:
Newborn screening—Tandem mass spectrometry identifies elevations in long-chain acylcarnitines (C14-C18).

The disorders cannot be differentiated by tandem mass spectrometry methods. A second dried-blood-spot filter paper card may be requested by the Newborn Screening Laboratory if the initial screening result is above the normal range. Infants with presumptive positive screening (critical) results require prompt follow up. If this occurred, the clinician would be contacted by the Metabolic Treatment Center. When notified of these results, the clinician should immediately check on the clinical status of the baby and facilitate referral to the Metabolic Treatment Center. The Metabolic Treatment Center will provide consultation and assistance with diagnostic testing.

Situations that risk metabolic decompensation:
Metabolic decompensation can be triggered by the catabolic processes that occur in the course of infections, after an immunization, increased physical activity, or with a prolonged period of fasting. Typical clinical features are lethargy, vomiting, hypoglycemia, metabolic acidosis, and cardiac decompensation.

Monitoring:
Clinical observation is the most important tool for monitoring patients with LCHADD. They should be observed and assessed for hepatic function, neurological status, recurrent vomiting, refusal to eat, increased lethargy, apnea, or seizures. In these situations, immediate evaluation in the emergency room is necessary. In situations of metabolic decompensation, hypoglycemia can develop but normal blood glucose does not rule out metabolic instability and should never be a reason to delay therapy. It is also important for the primary care provider and the Metabolic Treatment Center to develop an on-going collaborative relationship in caring for these patients.

Treatment:
- Avoid fasting.
- Feed at regular intervals during the day and limit overnight fasting.
- Should not go without food intake longer than 4 hours for the first 4 months of life, 6 hours for ages 4-8 months, and no longer than 8 hours thereafter.
• The Metabolic Treatment Center will determine the patient’s diet prescription that establishes the optimum percentage of fat, carbohydrate, and protein.
• Restrict long-chain fatty acids to 10% of total energy
• Carnitine supplements—monitor and add carnitine only if necessary; there are concerns that long-chain acylcarnitines may induce arrhythmias in some patients.
• Supplementation with Medium Chain Triglycerides Oil (MCT) provides 10-20% of total energy.
• Increased carbohydrate intake and cornstarch therapy is necessary during acute illness.
• The use of cornstarch therapy is an ongoing treatment and is even more necessary during acute illness.
• If the child is vomiting or refuses to eat, the child needs to be taken to an emergency room for IV administration of at least 10% dextrose. These patients may go on to develop metabolic acidosis or hyperammonemia, in addition to severe hypoglycemia.
• Cardiac and ophthalmologic status should be reviewed on a regular basis.
• Infants and children with LCHADD should have regularly scheduled visits at the Metabolic Treatment Center.
• LCHADD chronic management is complicated, as many children take a significant amount of time (days to weeks) to improve clinically even after their biochemical parameters have normalized. Particular problems include gradual improvement in mental status, hypotonia, hepatomegaly, and cardiomyopathy. It is important to be aware that, despite therapy, children with LCHADD have died or been left with chronic neurological, cardiac, and hepatic problems.
• The parents should have an emergency protocol with them at all times. This protocol can be provided by the Metabolic Treatment Center, and it should contain basic information about the disorder, necessary diagnostic investigations, and guidelines for treatment.

Illness:
• **Any** illness can potentially lead to metabolic decompensation.
• Prevention and/or early intervention are of particular importance.
• Consult with the Metabolic Treatment Center within 24 hours of the onset of the illness or at the time of hospitalization.
• Provide high-carbohydrate feedings including cornstarch.
• Avoid dehydration.
• Closely monitor blood glucose and intake; even if blood glucose is normal, metabolic decompensation can occur.

Immunization:
• Immunizations must be kept current.
• **All** children with LCHADD should have a yearly vaccine for influenza.
• There is no contraindication to any immunization because of LCHADD.
• Parents and physicians should be alerted to the need for immediate evaluation if high fever, lethargy, or vomiting occurs in the first 24 hours.
• After an immunization without any other clinical symptoms, administration of acetaminophen or ibuprofen is warranted.

Surgical/Surgical Procedures:
• Discuss any plans for surgical and dental procedures with the Metabolic Treatment Center.
• Infants and children with LCHADD can undergo necessary anesthetic/surgical procedures.
• Any surgical procedure constitutes a potentially catabolic situation.
• Any surgery should include hospitalization preoperatively and postoperatively.
• Preoperative fasting should be avoided, with 10% dextrose being started preoperatively and continuing postoperatively until the child is eating and drinking well.
• If complicated surgery or a postoperative period as an inpatient is anticipated, the procedure should be done at a hospital with a metabolic service.

Growth and Development:
• It is crucial to closely monitor all growth parameters on a regular basis.
• In cases with neurological deficits, the child should be referred to an early intervention program and developmental progress should be closely monitored by both the metabolic team and the primary care provider.

Note: A pregnant woman carrying a fetus with LCHADD is at risk for HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet counts) or acute fatty liver of pregnancy.
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Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCADD)

Description:
Medium Chain Acyl-CoA Dehydrogenase Deficiency is an autosomal recessive genetic condition. MCADD is caused by a defect in the MCAD enzyme, one of the enzymes involved in the mitochondrial beta-oxidation cycle. Individuals with this disorder are unable to break down fatty acids for use as an alternative energy source. Metabolic crisis can occur during periods of fasting and can cause episodes of hypoglycemia, vomiting, coma, and even death.

General Population Incidence:
1:25,000 live births

Symptoms:
Metabolic crisis may be precipitated by intercurrent illnesses and may present very quickly in infants/children who are not feeding properly. MCADD typically presents with hypoketotic hypoglycemia, lethargy, vomiting, seizures, coma or sudden death. Infants may be more subject to sudden death than older children. About 20% of infants with MCADD die during an acute episode when the diagnosis is not yet suspected. Survivors may suffer from neurological sequelae such as developmental delay, seizures, attention deficit hyperactive disorder or other behavioral abnormalities.

Diagnosis:
Newborn screening--Tandem mass spectrometry identifies elevations in medium chain acylcarnitines (C8-C8/C10 ratio).
The Newborn Screening Laboratory may request a second dried-blood-spot filter paper card if the initial screening result is above the normal range. Infants with presumptive positive screening (critical) results require prompt follow up. If this occurred, the clinician would be contacted by the Metabolic Treatment Center. When notified of these results, the clinician should immediately check on the clinical status of the baby and facilitate referral to the Metabolic Treatment Center. The Metabolic Treatment Center will provide consultation and assistance with diagnostic testing.

Situations that risk metabolic decompensation:
Children with MCADD are often clinically asymptomatic. Metabolic decompensation can be triggered by the catabolic processes that occur in the course of an infection, after an immunization or with a prolonged period of fasting.

Monitoring:
Clinical observation is the most important tool for monitoring patients with MCADD. They should be observed for recurrent vomiting, refusal to eat, increased lethargy, apnea or seizures. In these situations, immediate evaluation in the emergency room is necessary. In situations of metabolic decompensation hypoglycemia can develop, but a normal blood glucose does not rule out metabolic instability and should never be a reason to delay therapy. It is also important for the primary care provider and the Metabolic Treatment Center to develop an on-going collaborative relationship in caring for these patients.
Treatment:
- Avoid fasting
- Feed at regular intervals during the day and limit overnight fasting.
- Should not go without food intake longer than 4 hours for the first 4 months of life; 6 hours for ages 4-8 months; and no longer than 8 hours thereafter.
- Restriction of dietary fat is controversial but it is reasonable during intercurrent infections; The Metabolic Treatment Center will set a patient’s diet prescription that determines the optimum percentage of fat, carbohydrate, and protein.
- Carnitine supplements are provided in the case of a low blood carnitine level.
- Increased carbohydrate intake and cornstarch therapy is necessary during acute illness. The use of cornstarch therapy is an ongoing treatment and is even more necessary during acute illness.
- If the child is vomiting or refuses to eat, the child needs to be taken to an emergency room for IV administration of at least 10% dextrose.
- Infants and children with MCADD should have regularly scheduled visits at the Metabolic Treatment Center.
- The parents should have an emergency protocol with them at all times. This protocol can be provided by the Metabolic Treatment Center, and contains basic information about the disorder, necessary diagnostic investigations and guidelines for treatment.

Illness:
- Any illness can potentially lead to metabolic decompensation.
- Prevention and/or early intervention are of particular importance.
- Consult with the Metabolic Treatment Center within 24 hours of the onset of the illness or at the time of hospitalization.
- Provide high-carbohydrate feedings including cornstarch.
- Avoid dehydration.
- Closely monitor blood glucose and intake; even if blood glucose is normal, metabolic decompensation can occur.

Immunization:
- Immunizations must be kept current.
- All children with MCADD should have a yearly vaccine for influenza.
- There is no contraindication to any immunization because of MCADD.
- Parents and physicians should be alerted to the need for immediate evaluation if high fever, lethargy or vomiting occurs in the first 24 hours.
- After an immunization without any other clinical symptoms, administration of acetaminophen or ibuprofen is warranted.

Surgical/surgical procedures:
- Discuss any plans for surgical and dental procedures with the Metabolic Treatment Center.
- Infants and children with MCADD can undergo necessary anesthetic/surgical procedures.
- Any surgical procedure constitutes a potentially catabolic situation.
- Any surgery should include hospitalization pre- and postoperatively.
- Preoperative fasting should be avoided, with 10% dextrose being started preoperatively and continuing postoperatively until the child is eating and drinking well.
- If complicated surgery, or a postoperative period, as an inpatient is required, the procedure should be done at a hospital with a metabolic service.
**Growth and development:**
- It is crucial to closely monitor all growth parameters on a regular basis.
- In cases with neurological deficits, the child should be referred to an early intervention program and developmental progress closely monitored by both the metabolic team and the primary care provider.
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Trifunctional Protein Deficiency (TFPD)

Description:
Trifunctional Protein Deficiency is an autosomal recessive genetic condition caused by enzyme defects in the mitochondrial beta-oxidation cycle. Individuals with this disorder are unable to break down fatty acids into an energy source. Metabolic crisis can occur during periods of fasting and can cause episodes of hypoglycemia, vomiting, coma, and even death.

Incidence in General Population:
1:100,000 live births

Symptoms:
Metabolic crisis may be precipitated by intercurrent illnesses and may present with symptoms that include hypoglycemia, lethargy, failure to thrive, hypotonia, seizures, developmental delay, peripheral neuropathy, cardiomyopathy, coma, or sudden death. Severe, untreated cases may present as SIDS. Affected infants and children usually present by 2 years of age.

Diagnosis:
Newborn screening—Tandem mass spectrometry identifies elevations in long-chain acylcarnitines (C14-C18).
The disorder cannot be differentiated by tandem mass spectrometry methods.
A second dried-blood-spot filter paper card may be requested by the Newborn Screening Laboratory if the initial screening result is above the normal range. Infants with presumptive positive screening (critical) results require prompt follow up. If this occurred, the clinician would be contacted by the Metabolic Treatment Center. When notified of these results, the clinician should immediately check on the clinical status of the baby and facilitate referral to the Metabolic Treatment Center. The Metabolic Treatment Center will provide consultation and assistance with diagnostic testing.

Situations That Risk Metabolic Decompensation:
Metabolic decompensation can be triggered by the catabolic processes that occur in the course of infections, after an immunization, increased physical activity, or with a prolonged period of fasting. Typical clinical features are lethargy, vomiting, hypoglycemia, metabolic acidosis, and cardiac decompensation.

Monitoring:
Clinical observation is the most important tool for monitoring patients with TPD. They should be observed and assessed for hepatic function, neurological status, recurrent vomiting, refusal to eat, increased lethargy, apnea, or seizures. In these situations, immediate evaluation in the emergency room is necessary. In situations of metabolic decompensation, hypoglycemia can develop, but normal blood glucose does not rule out metabolic instability and should never be a reason to delay therapy. It is also important for the primary care provider and the Metabolic Treatment Center to develop an on-going collaborative relationship in caring for these patients.

Treatment:
- Avoid fasting.
- Feed at regular intervals during the day and limit overnight fasting.
- Should not go without food intake longer than 4 hours for the first 4 months of life, 6 hours for ages 4-8 months, and no longer than 8 hours thereafter.
The Metabolic Treatment Center will determine the patient’s diet prescription that establishes the optimum percentage of fat, carbohydrate, and protein.

- Restrict long-chain fatty acids to 10% of total energy
- Carnitine supplements—monitor and add carnitine only if necessary; there are concerns that long-chain acylcarnitines may induce arrhythmias in some patients.
- Supplementation with Medium Chain Triglycerides Oil (MCT) provides 10-20% of total energy.
- Increased carbohydrate intake and cornstarch therapy is necessary during acute illness. The use of cornstarch therapy is an ongoing treatment and is even more necessary during acute illness.
- If the child is vomiting or refuses to eat, the child needs to be taken to an emergency room for IV administration of at least 10% dextrose. These patients may go on to develop metabolic acidosis or hyperammonemia, in addition to severe hypoglycemia.
- Cardiac and ophthalmologic status should be reviewed on a regular basis.
- Infants and children with TPD should have regularly scheduled visits at the Metabolic Treatment Center.
- TPD chronic management is complicated, as many children take a significant amount of time (days to weeks) to improve clinically even after their biochemical parameters have normalized. Particular problems include gradual improvement in mental status, hypotonia, hepatomegaly, and cardiomyopathy. It is important to be aware that, despite therapy, children with TPD have died or been left with chronic neurological, cardiac, and hepatic problems.
- The parents should have an emergency protocol with them at all times. This protocol can be provided by the Metabolic Treatment Center, and it should contain basic information about the disorder, necessary diagnostic investigations, and guidelines for treatment.

**Illness:**
- **Any** illness can potentially lead to metabolic decompensation.
- Prevention and/or early intervention are of particular importance.
- Consult with the Metabolic Treatment Center within 24 hours of the onset of the illness or at the time of hospitalization.
- Provide high-carbohydrate feedings including cornstarch.
- Avoid dehydration.
- Closely monitor blood glucose and intake; even if blood glucose is normal, metabolic decompensation can occur.

**Immunization:**
- Immunizations must be kept current.
- All children with TPD should have a yearly vaccine for influenza.
- There is no contraindication to any immunization because of TPD.
- Parents and physicians should be alerted to the need for immediate evaluation if high fever, lethargy or vomiting occurs in the first 24 hours.
- After an immunization without any other clinical symptoms, administration of acetaminophen or ibuprofen is warranted.

**Surgical/Surgical Procedures:**
- Discuss any plans for surgical and dental procedures with the Metabolic Treatment Center.
- Infants and children with TPD can undergo necessary anesthetic/surgical procedures.
- Any surgical procedure constitutes a potentially catabolic situation.
- Any surgery should include hospitalization preoperatively and postoperatively.
- Preoperative fasting should be avoided, with 10% dextrose being started preoperatively and continuing postoperatively until the child is eating and drinking well.
• If complicated surgery or a postoperative period as an inpatient is anticipated, the procedure should be done at a hospital with a metabolic service.

Growth and Development:
• It is crucial to closely monitor all growth parameters on a regular basis.
• In cases with neurological deficits, the child should be referred to an early intervention program and developmental progress should be closely monitored by both the metabolic team and the primary care provider.

Note: A pregnant woman carrying a fetus with TFP is at risk for HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet counts) or acute fatty liver of pregnancy.
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FACT SHEET
Healthcare Provider

Very Long-Chain Acyl-CoA Dehydrogenase Deficiency (VLCADD)

Description:
Very Long-Chain Acyl-CoA Dehydrogenase Deficiency is an autosomal recessive disorder of fatty acid oxidation resulting in an inability to break down long-chain fatty acids because an enzyme is either missing or not functioning correctly. Reduced carbohydrate intake as a result of a prolonged fasting state or increased energy needs from a catabolic state (infection, stress, etc.) may cause metabolic decompensation if energy needs are not sufficiently provided for by increased caloric intake.

Incidence in General Population:
1:75,000 live births

Symptoms:
Because of the inability to utilize very long-chain fatty acids for energy production, prolonged fasting (more than 4 to 6 hours), intercurrent illness, and excessive activity make the child vulnerable to acute episodes of metabolic decompensation, hypoglycemia, coma, liver dysfunction, congestive heart failure, and hepatic encephalopathy. The initial presentation may occur in the neonatal period but more often when the infant is being weaned from nighttime feeds. The usual picture is vomiting and/or lethargy after a period of fasting. This can progress to hypoglycemic seizures or coma within 1-2 hours of onset of symptoms. There may be a history of a recent viral infection associated with diminished oral intake or of a similar episode in the past. Fatty acid oxidation disorders (FAODs) are responsible for a small but significant proportion of sudden infant death syndrome, which may be preventable with prompt recognition and treatment.

Diagnosis:
Newborn screening—Tandem mass spectrometry identifies elevations in plasma long-chain acylcarnitines (C14:1, C16, C18:1).
A second dried-blood-spot filter paper card may be requested by the Newborn Screening Laboratory if the initial screening result is above the normal range. Infants with presumptive positive screening (critical) results require prompt follow up. If this occurred, the clinician would be contacted by the Metabolic Treatment Center. When notified of these results, the clinician should immediately check on the clinical status of the baby and facilitate referral to the Metabolic Treatment Center. The Metabolic Treatment Center will provide consultation and assistance with diagnostic testing.

Situations That Risk Metabolic Decompensation:
Children with VLCADD may be clinically symptomatic. Metabolic decompensation can be triggered by the catabolic processes that occur in the course of an infection, post-immunization, or with a prolonged period of fasting. Lethargy, vomiting, tachypnea, or apnea, with or without hypoglycemia are typical clinical features.

Monitoring:
Clinical observation is the most important tool for monitoring patients with known VLCADD. They should be observed for lethargy, recurrent vomiting, refusal to eat, Tachypnea, or apnea. In these situations, immediate evaluation in the emergency room is necessary. In situations of metabolic decompensation, hypoglycemia with small or no urinary ketones can develop, but a normal blood glucose level does not rule out metabolic instability and should never be a reason to delay therapy.
Cardiac Evaluation:
Any child diagnosed with VLCADD should receive an immediate referral to a pediatric cardiologist for the presence of cardiomyopathy. Regular evaluations should occur thereafter for assessment of clinical symptoms suggestive of cardiomyopathy such as tachypnea, hepatomegaly, tachycardia, feeding problems, and exercise intolerance. However, it is important to know that cardiomyopathy can be present without any clinical symptoms.

Treatment:
- Avoid fasting and prolonged exercise.
- Feed at regular intervals during the day and limit overnight fasting.
- Children should not go without food intake longer than 4 hours for the first 4 months of life, 6 hours for ages 4-8 months, and no longer than 8 hours thereafter.
- The Metabolic Treatment Center will determine the patient’s diet prescription that establishes the optimum percentage of fat, carbohydrate, and protein.
- Restrict very long-chain fatty acids to 10% of total energy.
- Carnitine supplements—monitor blood levels and add carnitine supplementation only if necessary; there are concerns that long-chain acylcarnitines may induce arrhythmias.
- Supplementation with Medium Chain Triglycerides Oil (MCT) provides 10-20% of total energy.
- Increased carbohydrate intake and cornstarch therapy is necessary during acute illness. The use of cornstarch therapy is an ongoing treatment and is even more necessary during acute illness.

Illness and Immunizations:
- Any illness can potentially lead to metabolic decompensation.
- Prevention and/or early intervention is of particular importance.
- Provide high-carbohydrate feedings including cornstarch.
- Avoid dehydration.
- Closely monitor blood glucose and intake; even if blood glucose is normal, metabolic decompensation can occur.
- Immunizations must be kept current.
- All children with VLCADD should be annually vaccinated for influenza.
- There are no immunization contraindications because of VLCADD.
- Parents and physicians should be alert to the need for immediate evaluation if high fever, lethargy, or vomiting occurs within the first 24 hours.
- After an immunization with any other clinical symptoms, administration of acetaminophen or ibuprofen is warranted.

Surgical/Surgical Procedures:
- Discuss any plans for surgical and dental procedures with the Metabolic Treatment Center.
- Infants and children with VLCADD can undergo necessary anesthetic/surgical procedures.
- Any surgical procedure constitutes a potentially catabolic situation.
- Any surgery should include hospitalization preoperatively and postoperatively.
- Preoperative fasting should be avoided with 10% dextrose being started preoperatively and continuing postoperatively until the child is eating and drinking well.
- If complicated surgery or a postoperative period as an inpatient is required, the procedure should be done at a hospital with a metabolic service.
Growth and Development:

- It is crucial to closely monitor all growth parameters on a regular basis.
- In cases with neurological deficits, the child should be referred to an early intervention program and developmental progress should be closely monitored by both the metabolic team and the primary care provider.

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November 2005
Category: Organic Acid Disorders

Organic acidemias are inherited conditions that affect the way a person’s body uses protein. A person with an organic acidemia cannot properly break down certain components of protein for energy, growth, and development. Typically, these compounds are amino acids that are not completely broken down. Because the body cannot properly break down these amino acids certain organic acids build up in the blood and urine. High levels of certain organic acids can cause serious health problems. 

- Cobalamin A (cblA) and Cobalamin B (cblB)
- Methylmalonic CoA Mutase Deficiency aka MUT- and MUT°
- Beta-Ketothiolase Deficiency (Mitochondrial Acetoacetyl CoA Thiolase Deficiency) (BKT)
- Glutaric Acidemia Type I (GA I)
- 3-Hydroxy-3Methylglutaryl-CoA Lyase Deficiency (HMG)
- Isovaleric Acidemia (IVA)
- 3-Methylcrotonyl-CoA Carboxylase Deficiency (3MMC or 3MCC)
- Multiple CoA Carboxylase Deficiency (MCD)
- Propionic Acidemia (PPA)

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FACT SHEET
Healthcare Provider

Cobalamin A (cblA) and Cobalamin B (cblB)

Methylmalonic Acidemia (MMA)

Description:
Methylmalonic Acidemia is an autosomal recessive disorder. The incidence of both benign and severe forms is each about 1 in 50,000. MMA is caused by a deficiency of methylmalonyl-CoA mutase (MCM), a vitamin B12-dependent enzyme. The deficiency of MCM leads to accumulation of methylmalonyl-CoA, resulting in greatly increased amounts of methylmalonic acid in plasma and urine.

Incidence in General Population:
Cbl A& cblB—1:100,000 live births

Symptoms:
Dehydration and failure to thrive are generally the first signs of MMA. Symptoms usually begin in the first few months of life and include lethargy, vomiting, respiratory distress, hypotonia, and hepatomegaly. Acute episodes may include drowsiness, coma, and seizures, with subsequent developmental delays.

Methylmalonic acidemia can be expressed differently depending on the following:
- Defect in the synthesis of 5-deoxyadenosylcobalamin (cblA, cblB).
- Defect in cobalamin metabolism (cblC, cblD, cblF), which presents with both methylmalonic acidemia and homocystinuria.

Vitamin B12-responsive MMA patients can have a milder disease and a better clinical outcome. Conversely, Vitamin B12-unresponsive MMA patients have severe disease and many encephalopathic episodes. The early onset patients have the poorest survival rate. Survivors of both the early- and late-onset forms may have poor growth and neurologic sequelae with developmental delay and neurological impairment, and many older patients may have chronic renal failure.

Diagnosis:
Newborn screening abnormality—Tandem mass spectrometry:  
C3—elevated  
C4 DC—elevated

Confirmation—A second sample may be requested for confirmation of initial results. Follow-up testing will be done at the Metabolic Treatment Center.

Situations That Risk Metabolic Decompensation:
Protein catabolism can be caused by intercurrent infections, immunizations, trauma, anesthesia and surgery, fasting, dehydration, and dietary indiscretion. In cases of clinical deterioration with anorexia and/or gastric intolerance or if the child is obviously ill, the patient must be hospitalized to evaluate the clinical status and metabolic imbalance, to search for and treat intercurrent disease, and to halt protein catabolism. Emergency therapy depends on the presence of dehydration, acidosis, ketosis, and hyperammonemia.

Monitoring:
Clinical observation is the most important tool for monitoring patients with MMA. It is important for the primary care provider and the Metabolic Treatment Center to develop an on-going collaborative relationship in caring for these patients.
Treatment:
Long-term dietary treatment is aimed at reducing accumulated toxic metabolites while at the same time maintaining normal development and nutritional status and preventing catabolism. Some patients tolerate normal foods; others need only minimal restriction or can even regulate the diet themselves. However, many need very specific food allowances, implying stringent dietary restrictions that will likely be a life-long necessity.
- Precise prescriptions for the daily intake of amino acids, protein, and energy will be determined by the Metabolic Treatment Center.
- Frequent monitoring of clinical and metabolic status will be done.
- Enough water must be added to prevent dehydration of these patients who may have a low renal concentrating capacity and may not tolerate hyperosmolar formulas.
- Cobalamin and carnitine supplementation are suggested.
- Short-term treatment with oral metronidazole may improve alertness and appetite, while longer treatment periods have resulted in a decrease in the number and severity of acidotic episodes, increase in appetite, decreased vomiting, growth acceleration, and improved behavior.
- Infants and children with MMA should have regularly scheduled visits at the Metabolic Treatment Center.
- The parents should have an emergency protocol with them at all times. This protocol can be provided by the Metabolic Treatment Center, and it should contain basic information about the disorder, necessary diagnostic investigations, and guidelines for treatment.

Illness:
- Any illness can potentially lead to metabolic decompensation.
- Prevention and/or early intervention are of particular importance.
- Consult with the Metabolic Treatment Center within 24 hours of the onset of illness.

Immunization:
Immunizations must be kept current. Influenza vaccinations are also recommended.

Surgical/Surgical Procedures:
- Discuss any plans for surgical and dental procedures with the Metabolic Treatment Center.
- Any procedure requiring anesthesia should be done at a hospital with a metabolic service.

Growth and Development:
- It is crucial to closely monitor all growth, development, and biochemical parameters with a monthly evaluation on length, weight, and head circumference.
- The child should be referred to an early intervention program, and developmental progress should be closely monitored by both the metabolic team and the primary care provider.
- Regular assessment of developmental progress provides the opportunity for psychological support, as social and emotional needs are major elements of the overall therapy of the affected child and of the well being of the family.

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November 2005
Methy]malonic Acidemia (MMA)

Description:
Methy[malonic Acidemia is an autosomal recessive disorder. The incidence of both benign and severe forms is each about 1 in 50,000. MMA is caused by a deficiency of methy[malonyl-CoA mutase (MCM), a vitamin B12-dependent enzyme. The deficiency of MCM leads to accumulation of methy[malonyl-CoA, resulting in greatly increased amounts of methy[malonic acid in plasma and urine.

Incidence in General Population:
MUT- & MUT°—1:75,000 live births

Symptoms:
Dehydration and failure to thrive are generally the first signs of MMA. Symptoms usually begin in the first few months of life and include lethargy, vomiting, respiratory distress, hypotonia, and hepatomegaly. Acute episodes may include drowsiness, coma, and seizures, with subsequent developmental delays.

Methy[malonic acidemia can be expressed differently depending on the following:
- Absence of enzyme activity even when hydroxycobalamin is provided in excess (mut°).
- Reduction in enzyme activity but activity detectable when stimulated by a high concentration of hydroxycobalamin (mut°).

Vitamin B12-responsive MMA patients can have a milder disease and a better clinical outcome. Conversely, Vitamin B12-unresponsive MMA patients have severe disease and many encephalopathic episodes. The early onset patients have the poorest survival rate. Survivors of both the early- and late-onset forms may have poor growth and neurologic sequelae with developmental delay and neurological impairment, and many older patients present can have chronic renal failure.

Diagnosis:
Newborn screening abnormality—Tandem mass spectrometry: C3—elevated C4 DC—elevated

A second dried blood spot filter paper card may be requested by the Newborn Screening Laboratory if the initial screening result is above the normal range. Infants with presumptive positive screening (critical) results require prompt follow up. If this occurred, the clinician would be contacted by the Metabolic Treatment Center. When notified of these results, the clinician should immediately check on the clinical status of the baby and facilitate referral to the Metabolic Treatment Center. The Metabolic Treatment Center will provide consultation and assistance with diagnostic testing.

Situations That Risk Metabolic Decompensation:
Protein catabolism can be caused by intercurrent infections, immunizations, trauma, anesthesia and surgery, fasting, dehydration, and dietary indiscretion. In cases of clinical deterioration with anorexia and/or gastric intolerance or if the child is obviously ill, the patient must be hospitalized to evaluate the clinical status and metabolic imbalance, to search for and treat intercurrent disease, and to halt protein catabolism. Emergency therapy depends on the presence of dehydration, acidosi[s, ketosis, and hyperammonemia.
Monitoring:
Clinical observation is the most important tool for monitoring patients with MMA. It is important for the primary care provider and the Metabolic Treatment Center to develop an on-going collaborative relationship in caring for these patients.

Treatment:
Long-term dietary treatment is aimed at reducing accumulated toxic metabolites while at the same time maintaining normal development and nutritional status and preventing catabolism. Some patients tolerate normal foods; others need only minimal restriction or can even regulate the diet themselves. However, many need very specific food allowances, implying stringent dietary restrictions that will likely be a lifelong necessity.

- Precise prescriptions for the daily intake of amino acids, protein, and energy will be determined by the Metabolic Treatment Center.
- Frequent monitoring of clinical and metabolic status will be done.
- Enough water must be added to prevent dehydration of these patients who may have a low renal concentrating capacity and may not tolerate hyperosmolar formulas.
- Cobalamin and carnitine supplementation are suggested.
- Short-term treatment with oral metronidazole may improve alertness and appetite, while longer treatment periods have resulted in a decrease in the number and severity of acidotic episodes, increase in appetite, decreased vomiting, growth acceleration, and improved behavior.
- Infants and children with MMA should have regularly scheduled visits at the Metabolic Treatment Center.
- The parents should have an emergency protocol with them at all times. This protocol can be provided by the Metabolic Treatment Center, and it should contain basic information about the disorder, necessary diagnostic investigations, and guidelines for treatment.

Illness:
- Any illness can potentially lead to metabolic decompensation.
- Prevention and/or early intervention are of particular importance.
- Consult with the Metabolic Treatment Center within 24 hours of the onset of illness.

Immunization:
Immunizations must be kept current. Influenza vaccinations are also recommended.

Surgical/Surgical Procedures:
- Discuss any plans for surgical and dental procedures with the Metabolic Treatment Center.
- Any procedure requiring anesthesia should be done at a hospital with a metabolic service.

Growth and Development:
- It is crucial to closely monitor all growth, development, and biochemical parameters with a monthly evaluation on length, weight, and head circumference.
- The child should be referred to an early intervention program, and developmental progress should be closely monitored by both the metabolic team and the primary care provider.
- Regular assessment of developmental progress provides the opportunity for psychological support, as social and emotional needs are major elements of the overall therapy of the affected child and of the well being of the family.

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November 2005
Beta-Ketothiolase Deficiency (Mitochondrial Acetoacetyl CoA Thiolase Deficiency) (BKT)

Description:
Beta-ketothiolase deficiency is an inborn error of isoleucine catabolism characterized by urinary excretion of 2-methyl-3-hydroxybutyric acid, 2-methylacetoacetic acid, tiglylglycine, and 2-butanone.

Incidence in General Population:
1:100,000 live births

Symptoms:
The clinical manifestations range from an asymptomatic course to severe life threatening ketoacidosis with coma and cardiomyopathy. The onset of symptoms occurs in late infancy or childhood. The mean age at presentation is 15 months (range 3 days to 48 months). There are documented cases of asymptomatic patients with enzyme deficiency. Frequency of decompensation attacks decreases with age and decompensation is uncommon after the age of 10 years. Clinical outcome varies widely, with a few patients suffering severe psychomotor retardation or death as a result of their initial attack and others having normal development and no episodes of acidosis. Despite severe recurrent attacks, appropriate supportive care can result in normal development. Symptoms include intermittent episodes of severe metabolic acidosis and ketosis accompanied by vomiting (often hematemesis), diarrhea, and coma that may progress to death. There is great clinical variability between patients. Infancy is the period of highest risk for decompensation. Death or neurologic complications can occur. Clinical complications can include cardiomyopathy, prolonged QT interval, neutropenia, thrombocytopenia, poor weight gain, renal failure, and short stature. If neurologically intact, patients are normal between episodes.

Diagnosis:
Newborn screening abnormality—Tandem mass spectrometry: increased C5:1
A second dried blood spot filter paper card may be requested by the Newborn Screening Laboratory if the initial screening result is above the normal range. Infants with presumptive positive screening (critical) results require prompt follow up. If this occurred, the clinician would be contacted by the Metabolic Treatment Center. When notified of these results, the clinician should immediately check on the clinical status of the baby and facilitate referral to the Metabolic Treatment Center. The Metabolic Treatment Center will provide consultation and assistance with diagnostic testing.

Situations That Risk Metabolic Decompensation:
Metabolic decompensation can be triggered by the catabolic processes that occur in the course of infections, after an immunization, increased physical activity, dehydration, or with a prolonged period of fasting.

Monitoring:
- Clinical observation is the most important tool for monitoring patients with BKT. It is important for the primary care provider and the Metabolic Treatment Center to develop an ongoing collaborative relationship in caring for these patients.
- Carefully assess infants presenting with unexplained vomiting for signs of metabolic acidosis and ketosis; urinalysis is particularly important in this regard since neonates normally do not excrete large quantities of ketones.
Treatment:
- Acute management of the ketoacidosis is supportive with IV glucose and bicarbonate.
- Bicarbonate therapy is often required long term.
- Protein rich diets and ketogenic diets should be avoided.
- Carnitine supplementation can be used.
- The family should monitor urinary ketones to be alert for impending metabolic crisis.

Illness:
- Any illness can potentially lead to metabolic decompensation.
- Prevention and/or early intervention are of particular importance.
- Consult with the Metabolic Treatment Center within 24 hours of the onset of the illness.

Immunization:
- Immunizations must be kept current. Influenza vaccinations are also recommended.

Surgical/Surgical Procedures:
- Discuss any plans for surgical and dental procedures with the Metabolic Treatment Center.
- Any procedure requiring anesthesia should be done at a hospital with a metabolic service.

Growth and Development:
- It is critical to closely monitor all growth, development, and biochemical parameters on a regular basis.
- Normal development is possible with early diagnosis and treatment.
- The child should be referred to an early intervention program, and developmental progress should be closely monitored by both the metabolic team and the primary care provider.

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November 2005
**FACT SHEET**  
Healthcare Provider

**Glutaric Acidemia Type I (GA I)**

**Description:**
Glutaric acidemia, type I (GA-I) is an autosomal recessive inborn error of metabolism caused by the deficiency of glutaryl-CoA dehydrogenase, an essential enzyme in the catabolism of the amino acids tryptophan, lysine, and hydroxylysine. Some infants are symptomatic early, while in others the disorder may appear suddenly and present as a toxic encephalopathy after a period of apparently normal development.

**Incidence in General Population:**
1:75,000 live births

**Symptoms:**
This enzyme deficiency disorder is characterized by hypoglycemia, dystonia, and dyskinesia. Symptoms include vomiting, poor feeding, neurologic symptoms such as seizures and abnormal tone, and lethargy progressing to coma. Additional neurologic findings may include repetitive movements or abnormal posturing. Despite slow improvement, many patients do not fully recover from a neurologic crisis.

The most significant physical sign in GA-I is macrocephaly; in fact, macrocephaly may be the only physical sign in otherwise asymptomatic infants. Macrocephaly is present at or shortly after birth in 70% of infants who have GA I. Most commonly, infants develop progressive macrocephaly with markedly accelerated rates of head circumference growth in the first few months of life.

There are several different clinical presentations:
1. Affected infants appear normal and then suffer an acute metabolic crisis, usually 6 and 18 months of age, with subsequent neurological findings that improve slightly and then remain static. Changes in the basal ganglia, in particular atrophy of the caudate and putamen, develop within a few days or weeks of the encephalopathic episode. Neuronal loss and fibrous gliosis occur in the caudate and putamen as part of neurotoxicity of GA I.
2. Infants have a period of normal development, acute crisis, and subsequent neurological findings similar to those above, then progress slowly with recurrent episodes of ketosis, vomiting, hepatomegaly, and encephalopathy when the child develops infections.
3. Approximately 25% of infants gradually develop motor delay, hypotonia, dystonia, and dyskinesia during the first few years of life without any apparent acute crisis. Individuals can be completely asymptomatic without any crises and have normal development.

Neuroradiographic findings of frontal-temporal atrophy and/or arachnoid cysts before the onset of symptoms may be seen. Infants with GA-I are prone to suffer acute subdural hemorrhages and retinal hemorrhages after minor head trauma, i.e., commonly around the first birthday when starting to walk. This can be misdiagnosed as child abuse. In this population, 20-39% of patients have “chronic” subdural effusions and hematomas identified on neuroimaging studies; these are always found in the presence of atrophy and extra cerebral fluid.

**Diagnosis:**
Newborn screening abnormality—Tandem mass spectrometry: increased C5DC.
A second dried blood spot filter paper card may be requested by the Newborn Screening Laboratory if the initial screening result is above the normal range. Infants with presumptive positive screening (critical) results require prompt follow up. If this occurred, the clinician would be contacted by the Metabolic
Treatment Center. When notified of these results, the clinician should immediately check on the clinical status of the baby and facilitate referral to the Metabolic Treatment Center. The Metabolic Treatment Center will provide consultation and assistance with diagnostic testing.

Situations That Risk Metabolic Decompensation:
Fasting, intercurrent illness, post vaccination, and surgery.

Monitoring:
Clinical observation is the most important tool for monitoring patients with GA-I. It is important for the primary care provider and the Metabolic Treatment Center to develop an ongoing collaborative relationship in caring for these patients.

Treatment:
- Restricting dietary lysine and tryptophan rather than restricting total protein allows a greater intake of overall nitrogen.
- Pharmacologic doses of riboflavin, which serves as a cofactor for glutaryl-CoA dehydrogenase and facilitates any residual enzyme activity.
- Carnitine supplementation has been shown to increase the urinary excretion of glutaric acid and replenish reduced body carnitine stores.
- During an acute neurologic crisis, additional protein restriction and carbohydrate supplementation are introduced to prevent or reverse endogenous protein catabolism.
- The parents should have an emergency protocol with them at all times. This protocol can be provided by the Metabolic Treatment Center, and it should contain basic information about the disorder, necessary diagnostic investigations, and guidelines for treatment.
- Infants and children with GA-I should have regularly scheduled visits at the Metabolic Treatment Center.

Illness and Immunizations:
Intercurrent illnesses and vaccinations may aggravate hypotonia, unusual hand movements, and posturing but are usually reversible and of little clinical significance though they may precipitate crises (usually after the first birthday). Prevention and/or early intervention are of particular importance. For this and other reasons immunizations must be kept on track. There is no contraindication to immunization because of GA-I, but patients and physicians should be alerted to the need for immediate evaluation if high fever, lethargy, or vomiting occurs in the first 24 hours. The Metabolic Treatment Center should be consulted within 24 hours of the onset of the illness. Influenza vaccinations are also recommended.

Surgical/Surgical Procedures:
Preoperative fasting can precipitate encephalopathic crises.

Growth and Development:
Some patients may be intellectually intact; however, capabilities are dependent on avoidance of metabolic decompensation.

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November 2005
3-Hydroxy-3-Methylglutaryl-CoA Lyase Deficiency (HMG)

Description:
This disorder not only is a defect in the catabolism of leucine but also has an important role in ketone body metabolism. About one-third of individuals with HMG present in the neonatal period (2-5 days), and about two-thirds of individuals with HMG present between 3 and 11 months of age. There are reports of asymptomatic individuals detected because of an affected sibling. Between episodes the children are typically normal on exam. Instances of dilated cardiomyopathy with arrhythmia, pancreatitis, nonprogressive deafness, and retinitis pigmentosa have been reported. These may be related to neurological damage from the hypoglycemia.

Incidence in General Population:
1:100,000 live births

Symptoms:
The possibility of 3-Hydroxy-3-Methylglutaryl-CoA Lyase Deficiency should be considered in neonates and infants presenting with symptoms resembling Reye syndrome, neurologic dysfunction (such as obtundation, combativeness, and/or posturing), tachypnea, vomiting, hypoglycemia, hyperammonemia, hepatomegaly, and elevated transaminases in blood but without ketosis. Nonketotic hypoglycemia or hypoketotic hypoglycemia should raise the possibility of this disorder.

In the presence of catabolism or substantially reduced food intake (e.g., infection, severe exertion), the combination of an increased cellular requirement for energy and reduced glucose intake results in proteolysis with release of amino acids and fatty acids. Enhanced leucine and fatty acid degradation is an attempt by the body to produce the needed energy in the form of ketones. When 3-HMG-CoA lyase is deficient, the increases fluxes in both leucine degradation and fatty acid oxidation result in an accumulation of 3-hydroxymethylglutaryl-CoA. The accumulated substrate produces metabolic acidosis, inhibits gluconeogenesis resulting in hypoglycemia, and inhibits the urea cycle resulting in hyperammonemia.

Diagnosis:
Newborn screening abnormality—Tandem mass spectrometry: increased C5OH.
A second dried blood spot filter paper card may be requested by the Newborn Screening Laboratory if the initial screening result is above the normal range. Infants with presumptive positive screening (critical) results require prompt follow up. If this occurred, the clinician would be contacted by the Metabolic Treatment Center. When notified of these results, the clinician should immediately check on the clinical status of the baby and facilitate referral to the Metabolic Treatment Center. The Metabolic Treatment Center will provide consultation and assistance with diagnostic testing.

Situations That Risk Metabolic Decompensation:
Metabolic decompensation can be triggered by the catabolic processes that occur in the course of infections, after an immunization, increased physical activity, protein loading, dehydration, or with a prolonged period of fasting.

Monitoring:
Clinical observation is the most important tool for monitoring patients with HMG. They should be observed and assessed for neurological status, recurrent vomiting, refusal to eat, increased lethargy, apnea, or seizures. In these situations, immediate evaluation in the emergency room is necessary. In
situations of metabolic decompensation, hypoglycemia can develop but normal blood glucose does not rule out metabolic instability and should not be a reason to delay therapy. It is also important for the primary care provider and the Metabolic Treatment Center to develop an ongoing collaborative relationship in caring for these patients.

**Treatment:**
- Leucine restriction combined with general protein restriction. Fat intake restriction and avoidance of fasting with a high carbohydrate diet. Carnitine supplementation has been used, but its efficacy is unknown.
- The Metabolic Treatment Center will determine the patient’s diet prescription that establishes the optimum percentage of fat, carbohydrate, and protein.
- The parents should have an emergency protocol with them at all times. This protocol can be provided by the Metabolic Treatment Center, and it should contain basic information about the disorder, necessary diagnostic investigations, and guidelines for treatment.
- Infants and children with HMG should have regularly scheduled visits at the Metabolic Treatment Center.

**Illness:**
- Any illness can potentially lead to metabolic decompensation.
- Prevention and/or early intervention are of particular importance.
- Care should be coordinated by the Metabolic Treatment Center.

**Immunization:**
- Immunizations must be kept current. Influenza vaccinations are also recommended.

**Surgical/Surgical Procedures:**
- Discuss any plans for surgical and dental procedures with the Metabolic Treatment Center.
- A surgical procedure constitutes a potentially catabolic situation, and preoperative fasting should be avoided with 10% dextrose being started preoperatively and continuing postoperatively until the child is eating and drinking well. Any procedure requiring anesthesia should be done at a hospital with a metabolic service.

**Growth and development:**
- It is crucial to closely monitor all growth parameters on a regular basis.
- In cases with neurological deficits, the child should be referred to an early intervention program and developmental progress should be closely monitored by both the metabolic team and the primary care provider.
- Intellectual prognosis depends on early diagnosis and treatment and, subsequently, on compliance with the dietary and supplement plan.

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**VDH**

November 2005
Isovaleric Acidemia/ Isovaleric Aciduria (IVA)

Description:
IVA is an organic acid disorder caused by a deficiency of Isovaleryl-CoA dehydrogenase, an enzyme essential in the catabolism of the essential amino acid leucine. This genetic deficiency results in an accumulation of isovaleric acid, which is toxic to the central nervous system and leads to isovaleric acidemia. IVA occurs in both acute and chronic forms. Episodes can be triggered by infections or by excessive consumption of high-protein foods.

Incidence in General Population:
1:100,000 live births

Symptoms:
Infants with the acute neonatal form present at a few days of age with poor feeding, vomiting, severe metabolic keto-acidosis, progressing to coma and death. The infants are listless and lethargic and may be hypothermic. Tremors or twitching and convulsions may be seen. Dehydration, hyperammonemia, hypocalcemia, hepatomegaly, and hyper/hypoglycemia are often present. Depressed bone marrow function with neutropenia, thrombocytopenia and pancytopenia can lead to infection and/or cerebral hemorrhage. Most, but not all, will have the characteristic odor of “sweaty feet,” which comes from the accumulation of isovaleric acid.

The chronic intermittent form presents later in infancy or childhood with episodes of metabolic acidosis as described above, usually associated with an intercurrent illness or increased protein load. The recurrent episodes typically involve vomiting, lethargy progressing to coma, acidosis with ketonuria, and the characteristic odor of “sweaty feet.” The episodes resolve with protein restriction and infusion of glucose. The different forms can occur in the same family, so are not related to genotype. The biochemical defect is the same in both forms. Infants who survive the acute episode go on to exhibit the chronic form.

About 50% of patients with the acute neonatal form will die in their first episode. Survivors may have neurological damage, although several patients have had complete neurological recovery. Patients with the chronic form may have neurological damage, but most have normal growth and development. Death from episodes of decompensation can occur at any age.

As in most of the organic acidemias, the frequency of episodes is highest during infancy and subsequently decreases because of fewer infections and decreased protein intake, which naturally occurs with normal growth. Some patients develop a natural aversion to protein-rich foods.

Diagnosis:
Newborn screening abnormality—Tandem mass spectrometry: increased C5.
A second dried blood spot filter paper card may be requested by the Newborn Screening Laboratory if the initial screening result is above the normal range. Infants with presumptive positive screening (critical) results require prompt follow up. If this occurred, the clinician would be contacted by the Metabolic Treatment Center. When notified of these results, the clinician should immediately check on the clinical status of the baby and facilitate referral to the Metabolic Treatment Center. The Metabolic Treatment Center will provide consultation and assistance with diagnostic testing.
**Situations That Risk Metabolic Decompensation:**
Metabolic decompensation can be triggered by the catabolic processes that occur in the course of infections, after an immunization, increased physical activity, dehydration, or with a prolonged period of fasting.

**Monitoring:**
Clinical observation is the most important tool for monitoring patients with IVA. They should be observed and assessed for neurological status, recurrent vomiting, refusal to eat, increased lethargy, apnea, or seizures. In these situations, immediate evaluation in the emergency room is necessary. In situations of metabolic decompensation, hypoglycemia can develop but normal blood glucose does not rule out metabolic instability and should never be a reason to delay therapy. It is also important for the primary care provider and the Metabolic Treatment Center to develop an ongoing collaborative relationship in caring for these patients.

**Treatment:**
- Reduced-protein diet with restricted leucine intake, in combination with glycine and carnitine supplements. Glycine and carintine allow for the nontoxic removal of excess isovaleric-CoA.
- Patients will often self-select a low-protein diet.
- The Metabolic Treatment Center will determine the patient’s diet prescription that establishes the optimum percentage of fat, carbohydrate, and protein.
- The parents should have an emergency protocol with them at all times. This protocol can be provided by the Metabolic Treatment Center, and it should contain basic information about the disorder, necessary diagnostic investigations, and guidelines for treatment.
- Infants and children with IVA should have regularly scheduled visits at the Metabolic Treatment Center.

**Illness:**
- *Any* illness can potentially lead to metabolic decompensation.
- Prevention and/or early intervention are of particular importance.
- Care should be coordinated by the Metabolic Treatment Center.

**Immunization:**
- Immunizations must be kept current. Influenza vaccinations are also recommended.

**Surgical/Surgical Procedures:**
- Discuss any plans for surgical and dental procedures with the Metabolic Treatment Center.
- A surgical procedure constitutes a potentially catabolic situation, and preoperative fasting should be avoided with 10% dextrose being started preoperatively and continuing postoperatively until the child is eating and drinking well. Any procedure requiring anesthesia should be done at a hospital with a metabolic service.

**Growth and Development:**
- It is critical to closely monitor all growth parameters on a regular basis.
- In cases with neurological deficits, the child should be referred to an early intervention program and developmental progress should be closely monitored by both the metabolic team and the primary care provider.
- Intellectual progress depends on early diagnosis and treatment and, subsequently, on compliance with the dietary and supplement plan.

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November 2005
3-Methylcrotonyl-CoA Carboxylase Deficiency (3MMC or 3MCC)

Description:
3-Methylcrotonyl-CoA Carboxylase Deficiency is an autosomal recessive disorder of leucine catabolism. Deficiency of this enzyme results in an accumulation of 3-Methylcrotonyl-CoA.

Incidence in General Population:
1:75,000 live births

Symptoms:
Generally appear after 3 months of age but can be variable. Many individuals have no symptoms into adulthood. Some infants have presented with Reye-like illness with hypoketotic hypoglycemia, metabolic acidosis and liver dysfunction often precipitated by an intercurrent illness, which has led to fulminant liver failure and death in some cases. On other occasions infants present with hypotonia and failure-to-thrive in conjunction with recurrent episodes of vomiting and diarrhea. In general, the earlier symptoms present, the poorer the prognosis.

Diagnosis:
Newborn screening abnormality—(Tandem mass spectrometry): increased C5OH
A second dried blood spot filter paper card may be requested by the Newborn Screening Laboratory if the initial screening result is above the normal range. Infants with presumptive positive screening (critical) results require prompt follow up. If this occurred, the clinician would be contacted by the Metabolic Treatment Center. When notified of these results, the clinician should immediately check on the clinical status of the baby and facilitate referral to the Metabolic Treatment Center. The Metabolic Treatment Center will provide consultation and assistance with diagnostic testing.

Situations that risk metabolic decompensation:
Metabolic decompensation can be triggered by the catabolic processes that occur in the course of infections, after an immunization, increased physical activity, dehydration, or with a prolonged period of fasting.

Monitoring:
Clinical observation is the most important tool for monitoring patients with 3MCC. They should be observed and assessed for neurological status, recurrent vomiting, refusal to eat, increased lethargy, apnea or seizures. In these situations, immediate evaluation in the emergency room is necessary. In situations of metabolic decompensation, hypoglycemia can develop but normal blood glucose does not rule out metabolic instability and should not be a reason to delay therapy. It is also important for the primary care provider and the Metabolic Treatment Center to develop an ongoing collaborative relationship in caring for these patients.

Treatment:
- Reduced-protein diet with restricted leucine intake, in combination with glycine and carnitine supplements. Glycine and carnitine allow for the nontoxic removal of excess isovaleric-CoA.
- The Metabolic Treatment Center will determine the patient’s diet prescription that establishes the optimum percentage of fat, carbohydrate, and protein.
- The parents should have an emergency protocol with them at all times. This protocol can be provided by the Metabolic Treatment Center, and it should contain basic information about the disorder, necessary diagnostic investigations, and guidelines for treatment.
• Infants and children with 3MCC should have regularly scheduled visits at the Metabolic Treatment Center.

Illness:
• **Any** illness can potentially lead to metabolic decompensation.
• Prevention and/or early intervention are of particular importance.
• Care should be coordinated by the Metabolic Treatment Center.

Immunization:
Immunizations must be kept current, but patients and physicians should be alerted to the need for immediate evaluation if high fever, lethargy, or vomiting occurs in the first 24 hours. Influenza vaccinations are also recommended.

Surgical/surgical procedures:
• Discuss any plans for surgical and dental procedures with the Metabolic Treatment Center.
• A surgical procedure constitutes a potentially catabolic situation and preoperative fasting should be avoided with 10% dextrose being started preoperatively and continuing postoperatively until the child is eating and drinking well. Any procedure requiring anesthesia should be done at a hospital with a metabolic service.

Growth and development:
• It is crucial to closely monitor all growth parameters on a regular basis.
• In cases with neurological deficits, the child should be referred to an early intervention program and developmental progress should be closely monitored by both the metabolic team and the primary care provider.
• Intellectual prognosis depends on early diagnosis and treatment and, subsequently, on compliance with the dietary and supplement plan.
Multiple CoA Carboxylase Deficiency (MCD)

Description:
Multiple CoA Carboxylase Deficiency is an autosomal recessive metabolic disorder caused by a deficiency of the enzyme holocarboxylase synthase (HS). This deficiency leads to impaired activity of three enzymes that are dependent on biotin, part of the Vitamin B complex. Holocarboxylase synthetase (HS) attaches biotin to the four-carboxylase enzymes (pyruvate carboxylase, propionyl CoA carboxylase, beta-methylcrotonyl CoA carboxylase, and acetyl CoA carboxylase) in order to activate them. Deficiency in HS results in a functional decrease in the enzymatic activity of biotin-dependent carboxylases.

Incidence in General Population:
1:100,000 live births

Symptoms:
Symptoms include seizures, ketoacidosis, hypotonia, immune system impairment, a diffuse erythematous rash, alopecia, hearing loss and developmental retardation. The disorder occurs in both a neonatal and late-onset form and is treatable. Infants generally present with food refusal, vomiting, breathing problems, hypotonia, seizures, and lethargy. Severe metabolic/lactic acidosis, organic aciduria, mild hyperammonemia and variable hypoglycemia can lead to coma and death if not treated. Survivors can have neurological damage.

Diagnosis:
Newborn screening abnormality—Tandem mass spectrometry: increased C5OH. A second dried blood spot filter paper card may be requested by the Newborn Screening Laboratory if the initial screening result is above the normal range. Infants with presumptive positive screening (critical) results require prompt follow up. If this occurred, the clinician would be contacted by the Metabolic Treatment Center. When notified of these results, the clinician should immediately check on the clinical status of the baby and facilitate referral to the Metabolic Treatment Center. The Metabolic Treatment Center will provide consultation and assistance with diagnostic testing.

Treatment:
Treatment is oral biotin supplementation, which should begin immediately upon diagnosis. Majority of cases respond readily to biotin supplementation. Biotin increases the functional activation of the carboxylase enzymes.

Immunization:
Immunizations must be kept current. Influenza vaccinations are also recommended.

Growth and development:
Children with holocarboxylase synthetase deficiency treated with biotin can have normal growth and development. Biotin supplementation should be maintained through the lifetime of the affected individual. However, some partly respond to only therapy and one has been reported to be unresponsive to biotin therapy.

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Propionic Acidemia (PA)

Description:
Propionic academia is an autosomal recessive disorder of branched-chain amino acid metabolism in which a defective enzyme, propionyl-CoA carboxylase, results in an accumulation of propionic acid. In the United States, PA occurs in 1:20-100,000 live births.

Incidence in General Population:
1:75,000 live births

Symptoms:
Affected infants initially present in the first month of life, often with failure-to-thrive due to feeding intolerance and vomiting. Somnolence is often part of the history, so that poor feeding may be erroneously attributed to central nervous system disorders. Other infants have a fulminant initial presentation, with rapidly developing ketoacidosis, dehydration, shock, and a precedent history of lethargy, poor feeding, and rapid breathing that only extends over 1-2 days. Occasionally, an older infant or young child may have a lifelong history of episodic lethargy, anorexia, vomiting, and acidosis that has responded to short hospital stays with intravenous glucose and bicarbonate administration.

In patients who previously have been diagnosed with propionic academia, the acute onset of movement disorders caused by basal ganglia infarction may be a presenting feature. Dystonia, rigidity, choreoathetosis, and dementia in a child with a prior diagnosis of propionic academia suggest a basal ganglia infarction. While most children suffer neurologic damage during a metabolic crisis, rare cases without an identifiable precipitation factor have been reported. The metabolic crisis may result from changes in feeding or may be secondary to an infection.

Diagnosis:
Newborn screening abnormality—Tandem mass spectrometry: increased C3.
A second dried blood spot filter paper card may be requested by the Newborn Screening Laboratory if the initial screening result is above the normal range. Infants with presumptive positive screening (critical) results require prompt follow up. If this occurred, the clinician would be contacted by the Metabolic Treatment Center. When notified of these results, the clinician should immediately check on the clinical status of the baby and facilitate referral to the Metabolic Treatment Center. The Metabolic Treatment Center will provide consultation and assistance with diagnostic testing.

Situations That Risk Metabolic Decompensation:
Frequent episodes of decompensation can be devastating to the central nervous system. Any source of catabolic stress—such as vomiting, diarrhea, febrile illness, and decreased oral intake—can lead to decompensation, which requires prompt and aggressive intervention.

Monitoring:
- Clinical observation is the most important tool for monitoring patients with PA. It is important for the primary care provider and the Metabolic Treatment Center to develop an ongoing collaborative relationship in caring for these patients.
- Carefully assess infants presenting with unexplained vomiting for signs of ketoacidosis; urinalysis is particularly important in this regard since neonates normally do not excrete large quantities of ketones.
Central nervous system depression, signifying either severe acidosis or hyperammonemia, may be apparent on examination.

Any infant with an inborn error also can be affected by other disorders. Suspicion of sepsis based upon the typical nonspecific signs must not eliminate the possibility of underlying disease, such as propionic acidemia, for the differential.

Treatment:
- The use of specific metabolic foods (formulas) deficient in isoleucine, valine, threonine, and methionine is a critical part of management because such foods and formulas provide the essential amino acids in an otherwise protein-deficient diet. Adequate calories to inhibit catabolism are supplied as carbohydrate and fat, and appropriate protein must be supplied to support anabolism.
- The Metabolic Treatment Center will determine the patient’s diet prescription that establishes the optimum percentage of fat, carbohydrate, and protein.
- Carnitine supplementation may be a useful therapeutic adjunct to replete intracellular and extracellular stores of free carnitine.
- Use of adjunctive compounds to dispose of toxic metabolites and to increase activity of deficient enzymes and hemodialysis may be used during acute decompensation.
- Liver transplant may ameliorate the disease but does not completely eliminate the disorder because the kidneys are also involved in propionic acid metabolism.
- The parents should have an emergency protocol with them at all times. This protocol can be provided by the Metabolic Treatment Center, and it should contain basic information about the disorder, necessary diagnostic investigations, and guidelines for treatment.
- Infants and children with PA should have regularly scheduled visits at the Metabolic Treatment Center.

Illness:
- Any illness can potentially lead to metabolic decompensation.
- Prevention and/or early intervention are of particular importance.
- Consult with the Metabolic Treatment Center within 24 hours of the onset of the illness.

Immunization:
Immunizations must be kept current. Influenza vaccinations are also recommended.

Surgical/Surgical Procedures:
- Discuss any plans for surgical and dental procedures with the Metabolic Treatment Center.
- Any procedure requiring anesthesia should be done at a hospital with a metabolic service.

Growth and Development:
- It is crucial to closely monitor all growth, development, and biochemical parameters on a regular basis.
- The child should be referred to an early intervention program, and developmental progress should be closely monitored by both the metabolic team and the primary care provider.

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November 2005
Category: Other Metabolic Disorders

- Biotinidase Deficiency
- Galactosemia (GALT)
FACT SHEET
Healthcare Provider

Biotinidase Deficiency

Description:
Biotinidase deficiency is an autosomal recessive metabolic disorder. Biotinidase limits the liberation and recycling of the vitamin biotin. Deficiency of the enzyme biotinidase results in improper functioning of carboxylase enzymes essential to the body’s ability to alter fats and to metabolize carbohydrates and protein is impaired.

Incidence in General Population:
1:75,000 live births

Symptoms:
Severity
- Physical disabilities: seizures, skin rash, skin infection, alopecia, hypotonis, hearing loss, conjunctivitis, ataxia, breathing problem.
- Developmental disabilities: mental retardation, developmental delay.

Mortality
- Metabolic acidosis and organic acidemia can cause coma and death.

Variants
- Partial biotinidase deficiency is a milder form where activity of biotinidase is about 10-30% of the enzyme’s normal activity. Symptoms usually do not develop except under periods of stress from infection or poor diet.
- Symptomatic diagnosis is difficult because the age of onset of symptoms may be anywhere between 1 week and 10 years of age. Usually symptoms appear between 3 and 5 months of age.

Diagnosis:
Newborn screening—A qualitative colorimetric assay is used to determine the presence of the enzyme. In the presence of the enzyme, a color change occurs. A second dried-blood-spot filter paper card may be requested by the Newborn Screening Laboratory if the initial screening result is above the normal range. Infants with presumptive positive screening (critical) results require prompt follow up. If this occurred, the clinician would be contacted by the Metabolic Treatment Center. When notified of these results, the clinician should immediately check on the clinical status of the baby and facilitate referral to the Metabolic Treatment Center. The Metabolic Treatment Center will provide consultation and assistance with diagnostic testing.

Monitoring:
Clinical observation is important for healthcare providers caring for patients with Biotinidase. It is important for primary care provider and the Metabolic Center to develop an ongoing collaborative relationship in caring for these patients.

Treatment:
The acute symptoms of biotinidase deficiency will disappear with administration of pharmacological doses of oral biotin, usually between 5mg and 20mg per day. This provides the body with sufficient free biotin for all metabolic needs. Therapy is lifelong, and no dietary restrictions are necessary. Prognosis is good for children diagnosed with biotinidase deficiency prior to the occurrence of symptoms. No serious side effects of biotin treatment have been recognized.
**Illness and Immunizations:**
Immunizations should be kept current. Consult with the Metabolic Center within 24 hours of the onset of an illness or at the time of hospitalization.

**Growth and Development:**
Monitor child for normal growth and developmental milestones.

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November 2005
FACT SHEET
Healthcare Provider

Galactosemia (GALT)

Description:
The most common form of galactosemia, an autosomal recessive metabolic disorder, is the result of very little or absence of the enzyme galactose-1-phosphate uridyl transferase. This enzyme is involved in the digestion of galactose, a breakdown product of lactose. Lactose is present in milk and most infant formulas, and it naturally occurs in organ meats, legumes, fruits, and vegetables. Deficiency of galactose-1-phosphate uridyl transferase quickly raises the galactose content in the blood to dangerous levels.

Incidence in General Population:
1:50,000 live births

Symptoms:
Infants with galactosemia may appear normal at birth; within a few days to 2 weeks after initiating milk feedings, the symptoms of untreated galactosemia can become severe.

Severity
- Physical disabilities: cerebral palsy, ataxia, seizures, cataracts, and liver disease.
- Developmental disabilities: mental retardation.
- Mortality: liver failure, sepsis, or bleeding can cause severe morbidity and death.

Symptomatic diagnosis
- Symptoms can occur even before receiving the results of newborn screening. Early symptoms include jaundice, vomiting, lethargy, hepatosplenomegaly, cataracts, failure to thrive, hypoglycemia, and sepsis.

Variants
- Duarte Galactosemia is a milder form where activity of galactose-1-phosphate uridyl transferase is about 25-50% of the enzyme’s normal activity. Research has not revealed medical or other developmental complications associated with Duarte Galactosemia.

Diagnosis:
Newborn screening—Quantitative Flurometric testing is used to determine the presence of the galactose-1-phosphate uridyl transferase enzyme. In the absence of the enzyme, florescence (activity) does not occur. If there is no activity, a test for total galactose is performed. Several dried-blood-spot filter paper cards may be requested by the Newborn Screening Laboratory if the initial screening results are not within normal range. Infants with presumptive positive screening (critical) results require prompt follow up. If this occurred, the clinician would be contacted by the Metabolic Treatment Center. When notified of these results, the clinician should immediately check on the clinical status of the baby and facilitate referral to the Metabolic Treatment Center. The Metabolic Treatment Center will provide consultation and assistance with diagnostic testing.

Monitoring:
Individuals diagnosed with classical galactosemia require life-long medical management and dietary modification coordinated by nutrition and metabolic specialists. Clinical observation is important for healthcare providers caring for patients with classical galactosemia. It is important for primary care provider and the Metabolic Treatment Center to develop an ongoing collaborative relationship in caring for these patients.
Treatment:
Infants with galactosemia are started on milk-substituted formula, most likely a lactose-free soybean protein formula. Galactose is a non-essential nutrient, and individuals diagnosed with classical galactosemia require lactose-restricted diets for life. Endogenous production of galactose can complicate dietary treatment of galactosemia and may result in some developmental delays.

Illness and Immunizations:
Immunizations should be kept current. Consult with the Metabolic Treatment Center within 24 hours of the onset of an illness or at the time of hospitalization.

Surgical/Surgical Procedures:
Caution concerning administration of anesthesia and certain drugs that may contain lactose is necessary.

Growth and Development:
Monitor child for normal growth and developmental milestones.

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November 2005
Section 3.
Endocrine Disorders
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Endocrinology Consultants

The following physicians serve as consultants to Virginia Newborn Screening Services.

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Fact Sheets: Endocrine Disorders

The following fact sheets are intended to provide healthcare providers with an overview of all endocrine disorders that will be required screening effective March 1, 2006.

**Endocrine Disorder**
- Congenital Adrenal Hyperplasia (CAH)
- Congenital Hypothyroidism (CH)
**FACT SHEET**  
Healthcare Provider

**Congenital Adrenal Hyperplasia (CAH)**

**Description:**  
Congenital adrenal hyperplasia (CAH) is an autosomal recessive condition. CAH consists of a group of disorders arising from specific defects in the enzymes of the adrenal cortex required for the biosynthesis of adrenal corticosteroids. The most common form results from 21-hydroxylase deficiency, which accounts for more than 90% of all recognized cases. A child affected with CAH can go into adrenal crisis if they experience any stressors, such as an infection, an injury, or surgery. An adrenal crisis, or the complete failure to maintain normal balance, can result in death. In the most severely affected female newborn, the fetal adrenal androgens may masculinize the external genitalia to the extent that an incorrect male sex assignment is made. In approximately 75% of affected newborn boys, a life threatening “salt-wasting syndrome,” may be the only clinical finding leading to the correct diagnosis. Treatment prevents acute adrenal insufficiency by replacing the deficient steroid hormones and prevents the long-term consequences of excess virilization, advanced bone maturation leading to precocious puberty, and adult short stature by suppressing the excess adrenal androgens.

**Incidence in General Population:**  
1:25,000 live births

**Symptoms:**  
- Ambiguous genitalia in females  
- Enlarged penis and scrotum with increased pigmentation in males  
- Frequent urination  
- Poor feeding  
- Vomiting  
- Dehydration  
- Electrolyte changes  
- Cardiac arrhythmia  
- Precocious puberty  
- Premature skeletal maturation

**Newborn Screening Technology:**  
Detection by an immunofluorescent assay (IFA) for 17-hydroxy progesterone (17OHP). IFA first measures the level of 17 OHP in the blood. For infants whose 17-OHP is in either the highest 3% of results or above 40 ng/ml, the test result is confirmed by repeat testing. The interpretation of the generated 17-OHP result is then based on the infant’s birth weight.

**Diagnosis:**  
Measurement of serum 17-OH progesterone level and serum electrolytes is recommended along with referral to a pediatric endocrinologist. Early detection and treatment prevents adrenal insufficiency with dehydration, shock, and even death.

**Monitoring:**  
Lifelong monitoring, management, and compliance with treatment are essential to the child’s well being.
**Treatment:**
Lifetime daily medication of hydrocortisone in children and prednisone or dexamethasone for older individuals to replace missing cortisol. In cases of salt-wasting CAH, in addition to hydrocortisone, fludrocortisone is prescribed to correct aldosterone deficiency. Infants and small children with salt-wasting CAH also may require salt tablets as dietary supplement. Regulation of medication dosage is vital because improper dosage can result in either growth delay or premature bone epiphyseal closure. Female infants with ambiguous genitalia may require re-constructive surgery.

**Immunizations:**
Immunizations must be kept current

**Growth and development:**
It is crucial to closely monitor all growth parameters on a regular basis.

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FACT SHEET
Healthcare Provider

Congenital Hypothyroidism (CH)

Description:
Congenital Hypothyroidism (CH) is a condition in which the body does not secrete sufficient amounts of thyroid hormone. Because the body cannot produce an adequate amount of thyroid hormone, the pituitary will make additional thyroid stimulating hormone (TSH) in an attempt to entice the thyroid to produce more hormone. The causes for the lack of hormone production can be from agenesis, ectopic thyroid gland, or inherited disorders of thyroid hormone biosynthesis. If untreated, the symptoms of hypothyroidism will usually progress. Thyroxine deficiency in infancy can cause severe, irreversible mental and physical retardation, a condition known as cretinism. CH occurs sporadically and is not usually an inherited disorder. This disorder is not associated with any prenatal lifestyle or risk factors.

Incidence in General Population:
- 1:5,000 live births
- The occurrence is higher in the Hispanic and Native American ethnic groups. It is twice as common in females as in males. CH is more common in Caucasians than African Americans.

Symptoms:
- Feeding problems
- Lethargy
- Prolonged postnatal jaundice
- Delayed stooling and constipation
- Enlarged protruding tongue
- Course hair
- Cold intolerance
- Protruding abdomen
- Umbilical hernia
- Cold mottled skin
- Irritability
- Sluggish reflexes
- Patent posterior fontanelle
- Widely spread cranial sutures or delayed skeletal maturation for gestational age

Newborn Screening Technology:
Detection through an immunofluorescent assay (IFA) for thyroxine (T4) and thyroid stimulating hormones (TSH). IFA first measures the level of T4 in the blood. For infants whose T4 level falls in the lowest 10% of the results for the assay, TSH is measured on the same specimen. An elevated level of TSH indicates primary hypothyroidism, and the responsible physician is directed to have confirmatory T4 and TSH tests performed on a sample of the infant’s serum.

Diagnosis:
Collection of serum TSH and T4 levels is recommended along with referring infants to a pediatric endocrinologist for evaluation.

Monitoring:
Growth and development must be monitored at frequent intervals, including measurement of thyroid hormone levels to prevent both under and over treatment and their associated morbidities.
Treatment:
Early and adequate treatment and regular, careful monitoring is important to prevent permanent retardation of intellectual function and/or skeletal growth. With early treatment neurological development is comparable to peers without this diagnosis. Treatment for this disorder is lifelong. Medications should be prescribed and followed closely by a pediatric endocrinologist. Levothyroxine is given orally at a dosage to produce a T4 concentration in the upper normal range to normalize TSH levels. Tablets should be crushed daily; mixed with a few milliliters of water, formula, or breast milk; and fed to infant. Levothyroxine should not be mixed with soy formula or with formula containing iron, as these products interfere with absorption of the medication. Dosages of medication will need to be gradually increased as the infant grows.

Immunizations:
Immunization schedules should be followed to ensure protection from all other childhood diseases.

Growth and Development:
It is crucial to monitor all growth parameters on a regular basis.
Section 4.
Hemoglobinopathy Disorders
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Referral Components for Pediatric Comprehensive Sickle Cell Services in Virginia

The Virginia Sickle Cell Awareness Program is the state coordinating program for sickle cell education and adult screening services. The telephone number is (804) 864-7769. Regional referral sources for pediatric comprehensive care are presented below.

<table>
<thead>
<tr>
<th>Central Virginia</th>
<th>Contact Numbers</th>
</tr>
</thead>
</table>
| **Virginia Commonwealth University Health System** | Phone: (804) 828-9605  
Fax: (804) 828-0504 |
| Department of Pediatrics  
Division of Hematology/Oncology  
E. Clifton Russell, MD – Consultant  
P.O. Box 980121  
Richmond, Virginia 23298-0121 |

<table>
<thead>
<tr>
<th>Eastern Virginia</th>
<th>Contact Numbers</th>
</tr>
</thead>
</table>
| **Children’s Hospital of The King’s Daughters** | Phone: (757) 668-9783  
Fax: (757) 668-7811 |
| Department of Pediatrics  
Division of Hematology/Oncology  
William C. Owen, MD – Consultant  
Linda Pegram, MD – Consultant  
601 Children’s Lane  
Norfolk, Virginia 23507-1971 |

<table>
<thead>
<tr>
<th>Northern Virginia</th>
<th>Contact Numbers</th>
</tr>
</thead>
</table>
| **Pediatric Hematology and Oncology of Northern Virginia** | Phone: (703) 876-9111  
Fax: (703) 698-8338 |
| Jay Greenberg, MD, Consultant  
8301 Arlington Boulevard, Suite 209  
Fairfax, Virginia 22031 |
| **INOVA Fairfax Hospital** | Phone: (703) 876-2715  
Fax: (703) 876-2716 |
| Women and Children’s Center  
Comprehensive Sickle Cell Center  
3299 Woodburn Road – Suite 220  
Annandale, Virginia 22003 |

<table>
<thead>
<tr>
<th>Western Virginia</th>
<th>Contact Numbers</th>
</tr>
</thead>
</table>
| **University of Virginia Medical Center** | Phone: (434) 492-8499  
Fax: (434) 924.5452 |
| Department of Pediatrics, Hematology/Oncology  
Peter Waldron, MD - Consultant  
P.O. Box 800386 HSC, University of Virginia  
Charlottesville, Virginia 22908 |
| **Carilion Roanoke Community Hospital** | Phone: (540) 985-8055  
Fax: (540) 985-5306 |
| Department of Pediatrics  
Division of Hematology/Oncology  
Joan Fisher, MD, Ph.D., Consultant  
102 Highland Avenue, Suite 435  
Roanoke, Virginia 24029-2946 |
Fact Sheets: Hemoglobinopathy Disorders

The following fact sheets are intended to provide healthcare providers with an overview of all hemoglobinopathy disorders that will be required screening effective March 1, 2006.

- Sickle Cell Disease
- Other Hemoglobinopathies: F, FC, FCA, FE, FEA, FV, Barts
- Hemoglobin Trait Conditions: F/A/S, F/A/C, F/A/E, F/A/D, F/A/Barts
FACT SHEET
Healthcare Provider

Sickle Cell Disease

Description:
Hemoglobinopathies are a group of autosomal recessive disorders characterized by synthesis of abnormal hemoglobin molecules (e.g., S, E, C) or decreased synthesis of alpha or beta globin chains.

Sickle cell disease (SCD) is a collective term for a group of genetic disorders characterized by the predominance of hemoglobin S (Hb S). These disorders include sickle cell anemia (SS), the sickle beta thalassemia syndromes (Sβ+ or Sβ0), and hemoglobinopathies in which Hb S is present in combination with another variant hemoglobin. The most common examples include hemoglobin SC disease, hemoglobin SD disease, and hemoglobin SE disease.

There are two main pathophysiologic features of sickle cell disorders: chronic hemolytic anemia and vasoocclusion. Hemolytic anemia may be related to repeat cycles of sickling and unsickling, which interact to produce irreversible red cell membrane changes, red cell dehydration, and erythrocyte destruction. Tissue injury is usually produced by ischemia and infarction. The organs at greatest risk are those with venous sinuses where blood flow is slow and oxygen tension and pH are low (e.g., spleen and bone marrow) or those with a limited terminal arterial blood supply (e.g., eye, head of the femur and humerus). No tissue or organ is spared from this injury. Symptoms of the hypoxic injury may be either acute (e.g., painful events, acute chest syndrome) or insidious in onset (e.g., aseptic necrosis of the hips, sickle cell retinopathy). The effects of acute and chronic tissue injury may ultimately result in failure of organs like the kidney, particularly as the patient ages.

Symptoms:
The clinical course of sickle cell anemia does not follow a single pattern; some patients have mild symptoms, while others have very severe symptoms. Symptoms may be less severe or different in children who have inherited a sickle cell gene from one parent and a different abnormal hemoglobin gene from the other. Complications may include, but are not limited to, the following:

• **Hand-foot syndrome**: Dactylitis is the most common first sign of sickle cell disease in some infants. Signs include painful swelling of the hands and feet.

• **Infection**: Children with sickle cell disease are at increased risk for certain bacterial infections. It is important to watch for fevers of 101 degrees Fahrenheit (38.33 degrees Celsius) or higher, which could signal an infection. A clinician should see children with sickle cell disease and fever immediately.

• **Splenic sequestration crises**: Sickled red blood cells become trapped in the spleen, leading to fewer cells in the general circulation. Any enlargement of the spleen is of concern and must be watched for changes. Early signs include oral pallor, lethargy, an enlarged spleen, and pain in the abdomen.

• **Painful crises**: These may occur in any part of a child's body. Body cooling, fever, or dehydration may be triggers. Pain may last a few hours or up to 2 weeks or even longer.

• **Acute chest syndrome**: ACS is a result of sickling in the lungs and is associated with a new infiltrate on chest x-ray. Symptoms of ACS include cough, chest pain, fever, sputum production, dyspnea, or hypoxia. Infection is the most common identified cause, but pain is a frequent preceding event. Symptoms require emergency evaluation and treatment. This condition develops more often in young children but is usually more severe in adults.

• **Aplastic crisis**: Aplastic sickle cell crises occur when the bone marrow temporarily shuts down. The causative agent is usually human parvovirus B19. Because of the shortened red cell survival, marrow shutdown leads to profound anemia over a period of a few days. Signs include paleness and fatigue.
Parental education is very important so that they learn to recognize this condition early and seek medical treatment.

- **Stroke:** Decreased blood flow to the brain can occur from the sickle-shaped cells blocking small blood vessels. This may lead to a stroke. Signs may include headache, seizures, weakness of the arms and legs, speech problems, a facial droop, and loss of consciousness. Other possible complications include; leg ulcers, bone or joint damage, gallstones, kidney damage, priapism, eye damage, and delayed growth.

**Incidence in General Population:**
Sickle cell disease affects millions worldwide. It is particularly common among people whose ancestors come from sub-Saharan Africa; Spanish-speaking regions (South America, Cuba, Central America); Saudi Arabia; India; and Mediterranean countries such as Turkey, Greece, and Italy. In the United States, it affects around 72,000 people, most of whose ancestors come from Africa. The disease occurs in about 1 in every 350 African-American births and 1 in every 1,000 to 1,400 Hispanic-American births. About 2 million Americans, or 1 in 12 African Americans, carry the sickle cell trait.

**Diagnosis:**
Screening for sickle cell disease is done using dried-blood-spot screening tests. All first filter paper samples are screened for hemoglobinopathies using Isoelectric focusing (IEF). Various hemoglobin patterns occur. If an abnormality is detected, the sample is reanalyzed using high performance liquid chromatography (HPLC). A fresh sample is requested for confirmation of critical lab results. Family studies are needed to differentiate between homozygous sickle cell anemia and sickle beta^0^ thalassemia.

**Monitoring:**
Health care monitoring and maintenance with appropriate immunizations is imperative to the health of the infant with sickle cell disease. Newborns should be referred to a Pediatric Comprehensive Sickle Cell Center for ongoing disease management, parent education, and genetic counseling after a diagnosis of sickle cell disease has been confirmed. It is important that the primary care provider and the Comprehensive Sickle Cell Center develop an ongoing, collaborative relationship in caring for these patients. Please see Table 1 for suggested routine clinical laboratory evaluations.

**Table 1. Suggested Routine Clinical Laboratory Evaluations**

<table>
<thead>
<tr>
<th>Tests</th>
<th>Age</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC with WBC differential</td>
<td>3 mo – 24 mo</td>
<td>every 3 mo</td>
</tr>
<tr>
<td>Reticulocyte count</td>
<td>&gt;24mo</td>
<td>every 6 mo</td>
</tr>
<tr>
<td>Percent Hb F</td>
<td>12 mo – 24 mo</td>
<td>annually</td>
</tr>
<tr>
<td>Renal function (creatinine, BUN, urinalysis)</td>
<td>&gt;24 mo</td>
<td>every 12 mo</td>
</tr>
<tr>
<td>Hepatobiliary function (ALT, fractionated bilirubin)</td>
<td>&gt;12 mo</td>
<td>annually</td>
</tr>
<tr>
<td>Pulmonary function (transcutaneous O_2_ saturation)</td>
<td>&gt;12 mo</td>
<td>annually</td>
</tr>
</tbody>
</table>

**Transcranial Doppler ultrasonography (TCD),** magnetic resonance imaging (MRI) with or without angiography, and neuropsychometric (NPM) studies have been used extensively to evaluate children with SCD. An abnormally high blood flow velocity by TCD in the middle cerebral or internal carotid arteries is associated with an increased risk of stroke; however, blood flow results should be interpreted cautiously because they are dependent on the technique employed. TCD screening of children with homozygous sickle cell disease (SS) is recommended to start at 2 years of age and continue annually until 16 years of age if TCD is normal and every 4 months if TCD is marginal. Abnormal results should be repeated within 2 to 4 weeks. Children with SCD who have "silent" cerebral infarcts detected by MRI have a higher rate of abnormal NPM studies and a higher risk for overt strokes. Stroke prevention strategies based on
abnormal MRI results have not been tested, but children with abnormal MRI or NPM studies could be evaluated more frequently and carefully and considered for therapeutic measures.

**Pulmonary function tests (PFT)** should be done regularly in those with history of recurrent acute chest episodes or low oxygen saturation. Lung function declines with age, so it is important to identify those who need close monitoring and treatment.

**Treatment:**
Any sign of illness in an infant with sickle cell disease is a potential medical emergency. The most important intervention in the routine management of children with SCD is penicillin prophylaxis to prevent pneumococcal infection. The National Institutes of Health clinical guidelines for management of sickle cell disease state, "Penicillin prophylaxis should begin by 2 months of age for infants with suspected sickle cell anemia, whether or not the definitive diagnosis has been established." Antibiotic therapy should continue until at least 5 years of age. Normal dosage for an infant is 125 mg of penicillin twice a day until 3 years of age, when dosage is increased to 250 mg twice a day. Prescription pain medication may be indicated during a vasoocclusive event.

Hydroxyurea, a cancer medication, has been shown to reduce complications in sickle cell anemia by reducing the frequency of painful crises and episodes of acute chest syndrome. Currently, researchers are studying a number of new drug treatments for reducing complications of the disease.

Additional treatments may include:
- Partial exchange transfusion for acute chest syndrome.
- Transfusions or surgery for neurological events, such as strokes.
- Dialysis or kidney transplant for kidney disease.
- Irrigation or surgery for priapism.
- Surgery for eye problems.
- Hip replacement for avascular necrosis of the hip (death of the joint).
- Gallbladder removal (if there is significant gallstone disease).
- Wound care, zinc oxide, or surgery for leg ulcers.

Bone marrow transplants can be curative; however, this therapy is indicated in only a minority of patients due to the high risk of the procedure and difficulty in finding suitable donors.

**Immunizations:**
In addition to routine immunizations, children with SCD require additional immunizations. The recent introduction of the pneumococcal conjugated vaccine (PCV) is important for those with SCD. Prevnar (Wyeth-Lederle), the 7-valent PCV (PCV7) licensed in the United States, covers pneumococcal serotypes 4, 9V, 14, 19F, 23F, 18C, and 6B, and has possible cross-reactivity with serotypes 6A, 9A, 9L, 18B, and 18F. Together these serotypes account for 87% of bacteremia and 83% of meningitis due to pneumococcus in the United States. The American Academy of Pediatrics (AAP) recommends Prevnar for children with SCD up to 59 months of age. Please see Table 2 for the recommended schedule of pneumococcal immunizations for previously unvaccinated children with SCD. Please see Table 2 for the recommended schedule of pneumococcal immunizations for previously unvaccinated children with SCD.
Table 2. Recommended Schedule of Pneumococcal Immunizations for Previously Unvaccinated Children With Sickle Cell Disease

<table>
<thead>
<tr>
<th>Product Type</th>
<th>Age at 1st dose</th>
<th>Primary Series</th>
<th>Additional Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCV7 (Prevnar)</td>
<td>2-6 mo</td>
<td>3 doses 6-8 wk apart</td>
<td>1 dose at 12 to &lt;16 mo</td>
</tr>
<tr>
<td></td>
<td>7-11 mo</td>
<td>2 doses 6-8 wk apart</td>
<td>1 dose at 12 to &lt;16 mo</td>
</tr>
<tr>
<td></td>
<td>&gt; 12 mo</td>
<td>2 doses 6-8 wk apart</td>
<td>--</td>
</tr>
<tr>
<td>PPV23 (Pneumovax)</td>
<td>&gt; 24 mo</td>
<td>1 dose at least 6-8 wk after last PCV7 dose</td>
<td>1 dose 3-5 yr after first PPV23 dose</td>
</tr>
</tbody>
</table>

Growth and Development:
Delayed growth and puberty in children is dependant upon the severity of anemia.

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FACT SHEET
Healthcare Provider

Other Hemoglobinopathies:
F, FC, FCA, FE, FEA, FV, Barts

Description:
Other hemoglobinopathies are comprised of a non-sickling group of disorders characterized by anemia secondary to hemolysis and/or ineffective erythropoiesis.

Incidence in General Population:
- Hemoglobin C is most commonly affects people of African descent. It occurs in approximately 5% of African Americans. It also occurs in people of Hispanic, Italian, and Middle Eastern background.
- Hemoglobin E is the third most prevalent hemoglobin identified worldwide. It is most prevalent in South East Asians. Incidence in North Americans of European Ancestry: 1: 70,000.
- Variant Hemoglobin incidence is unknown.
- Hemoglobin Barts is commonly found in people of Asian decent, certain types of alpha thalassemia are also present in people of African decent.

Symptoms: Varying degrees of anemia and hemolysis. (See Table 1)
- **Hemoglobin F:** Infants with only Hb F may be normal infants who do not yet show Hb A because of prematurity or may have thalassemia major or another thalassemia syndrome. Infants with no Hb A need repeat testing. Homozygous Beta–thalassemia (Cooley’s Anemia) may cause severe transfusion dependent anemia.
- **Hemoglobin F/C:** Infants with a newborn genotype of F/C require family studies, utilizing hemoglobin electrophoresis and A2 quanitation to identify the carrier type of each parent to differentiate between homozygous Hb C Disease and Hb C Beta\(^0\) thalassemia. Both cause mild microcytic hemolytic anemia.
- **Hemoglobin F/C/A (Probable C Beta\(^+\) thalassemia):** Mild microcytic hemolytic anemia. A family study or repeat screening on the infant after 12 months utilizing hemoglobin electrophoresis and A2 quanitation will confirm the diagnosis.
- **Hemoglobin F/E:** Infants with a newborn genotype of F/E require family studies, utilizing hemoglobin electrophoresis and A2 quanitation to identify the carrier type of each parent to differentiate between homozygous Hb E, causes microcytosis and mild anemia, and Hb E Beta\(^0\) thalassemia, which is variably severe.
- **Hemoglobin F/E/A (Probable E Beta\(^+\) Thalassemia):** Mild microcytic hemolytic anemia. A family study or repeat screening on the infant after 12 months utilizing hemoglobin electrophoresis and A2 quanitation will confirm the diagnosis.
- **Hemoglobin F/V:** Unknown variant that may or may not be clinically significant. No national consensus has yet been produced to guide neonatal screening programs and clinicians in the follow up of infants with unidentified hemoglobin variants. However, some recommend repeat IEF, HPLC or hemoglobin electrophoresis and/or obtaining a CBC, reticulocyte count, and peripheral smear for red cell morphology between 6 and 12 months of age. Identification of the hemoglobin variant to clarify genetic risks is recommended for families in which another hemoglobin variant (e.g., Hb S) is present.
Table 1. Non-Sickle Hemoglobinopathies Identified by Neonatal Screening

<table>
<thead>
<tr>
<th>Screening Results</th>
<th>Possible Condition</th>
<th>Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin F only</td>
<td>Premature Infant</td>
<td>Repeat Screening</td>
</tr>
<tr>
<td></td>
<td>Homozygous $\beta^0$ Thalassemia</td>
<td>Severe thalassemia</td>
</tr>
<tr>
<td>FE</td>
<td>$\alpha$ $\beta^0$ Thalassemia</td>
<td>Microcytosis with mild or no anemia</td>
</tr>
<tr>
<td></td>
<td>E $\beta^0$ Thalassemia</td>
<td>Mild to severe anemia</td>
</tr>
<tr>
<td>FEA</td>
<td>$\alpha$ $\beta^0$ Thalassemia</td>
<td>Mild microcytic hemolytic anemia</td>
</tr>
<tr>
<td>FC</td>
<td>$\alpha$ C $\beta^0$ Thalassemia</td>
<td>Mild microcytic hemolytic anemia</td>
</tr>
<tr>
<td></td>
<td>C $\beta^0$ Thalassemia</td>
<td></td>
</tr>
<tr>
<td>FCA</td>
<td>Unknown variant</td>
<td>Unknown</td>
</tr>
<tr>
<td>FV</td>
<td>Unknown variant</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Hemoglobin Barts and Alpha Thalassemia Syndromes: Hemoglobin Barts is a tetramer of gamma (fetal) globin chains seen during the newborn period. Its presence indicates that one or more of the four genes that produce alpha globin chains is dysfunctional. Alpha Thalassemia is caused by a decrease in production of alpha globin chains due to a deletion or mutation of one or more of the four alpha globin genes located on chromosome 16. Alpha thalassemia occurs in individuals of all ethnic backgrounds and is one of the most common genetic diseases worldwide. The clinically significant forms, Hemoglobin H Disease and Alpha Thalassemia Major, occur predominately among Southeast Asians.

Table 2. Classification of Alpha Syndromes

<table>
<thead>
<tr>
<th>Gene deletion</th>
<th>Possible Condition</th>
<th>Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single gene deletion</td>
<td>Silent carrier</td>
<td>None</td>
</tr>
<tr>
<td>Two gene deletion</td>
<td>Alpha thalassemia trait</td>
<td>Mild anemia with microcytosis</td>
</tr>
<tr>
<td>Three gene deletion</td>
<td>Hemoglobin H Disease</td>
<td>Mild to moderately severe Microcytic hemolytic anemia</td>
</tr>
<tr>
<td>Four gene deletion</td>
<td>Severe fetal anemia</td>
<td>Fetal hydrops and death</td>
</tr>
</tbody>
</table>

Diagnosis:
Screening for sickle cell disease and other hemoglobinopathies is done using dried-blood-spot screening tests. All first filter paper samples are screened for hemoglobinopathies using Isoelectric Focusing (IEF). Various hemoglobin patterns occur. If an abnormality is detected, the sample is reanalyzed using high performance liquid chromatography (HPLC). A fresh sample is requested for confirmation of critical lab results.

- Family studies are needed to differentiate between hemoglobin E disease and E Beta$^0$ Thalassemia, hemoglobin C disease and C Beta$^0$ Thalassemia.
- Unknown variant hemoglobins and alpha thalassemia syndromes require globin chain analysis for definitive diagnosis. Infants identified with Barts hemoglobin should have a CBC done between 9 and 12 months. A normal MCV value indicates a single gene deletion and requires no medical follow-up; a low MCV indicates a two-gene deletion and requires no further medical follow-up.

Monitoring:
Newborns identified with hemoglobin F only, should be evaluated immediately by a hematologist. Parents should be screened for beta thalassemia trait. Newborns identified with FC, FCA, FE, FEA Hemoglobin H Disease, and FV, should be referred to a hematologist for routine evaluation. Care by an ophthalmologist may be needed for possible eye problems. Newborns suspected of having Hemoglobin H Disease should be monitored for severe anemia, enlarged spleen and bone deformities.

Immunizations:
Immunizations must be kept current.
Treatment:
Folic acid may help with the production of normal red blood cells and supplementation may improve the symptoms of the anemia. Newborns diagnosed with Beta Thalassemia Major (Hemoglobin F only) require regular blood transfusions. Bone marrow transplant provides the only cure for thalassemia.

Growth and Development:
Monitor child for normal growth and developmental milestones.

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November 2005
FACT SHEET
Healthcare Provider

Hemoglobin Trait Conditions:
F/A/S, F/A/C, F/A/E, F/A/D, F/A/Barts

Description:
Individuals with one abnormal beta globin or hemoglobin chain and one normal beta globin or
hemoglobin chain (heterozygotes) are said to have a "trait."

Incidence in General Population:
- Hemoglobin S It is particularly common among people whose ancestors come from sub-Saharan
  Africa; Spanish-speaking regions (South America, Cuba, Central America); Saudi Arabia; India; and
  Mediterranean countries such as Turkey, Greece, and Italy. In the United States, it affects around
  72,000 people, most of whose ancestors come from Africa. The disease occurs in about 1 in every
  350 African-American births and 1 in every 1,000 to 1,400 Hispanic-American births. About 2
  million Americans, or 1 in 12 African Americans, carry the sickle cell trait.
- Hemoglobin C is most commonly affects people of African descent. It occurs in approximately 5%
  of African Americans. It also occurs in people of Hispanic, Italian, and Middle Eastern background.
- Hemoglobin E is the third most prevalent hemoglobin identified worldwide. It is most prevalent in
  South East Asians. Incidence in North Americans of European Ancestry: 1: 70,000.
- Variant Hemoglobin incidence is unknown.
- The highest frequency of alpha thalassemia occurs in individuals of Southeast Asian and Chinese
descent. Individuals of Greek, Middle Eastern, and North African descent also carry genes for the
disease more frequently than individuals of Northern European descent. In the United States, up to 30
percent of African Americans are thought to be carriers for alpha thalassemia traits.

Symptoms:
Most hemoglobin traits are associated with few or no clinical symptoms. Trait detection provides the
opportunity to educate families, to test other family members, and to refer for genetic counseling.

Table 1. Common Newborn Hemoglobin Types

<table>
<thead>
<tr>
<th>Laboratory Result</th>
<th>Diagnosis</th>
<th>Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>Normal hemoglobin in newborn</td>
<td>None</td>
</tr>
<tr>
<td>FAS</td>
<td>Sickle cell trait in the newborn</td>
<td>Normal CBC, Generally asymptomatic</td>
</tr>
<tr>
<td>FAC</td>
<td>Hemoglobin C trait</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>FAE</td>
<td>Hemoglobin E trait</td>
<td>Asymptomatic, may have slightly lower MCV</td>
</tr>
<tr>
<td>F A/Barts</td>
<td>Probably Alpha Thal Trait</td>
<td>Mild anemia with microcytosis</td>
</tr>
<tr>
<td>FAV</td>
<td>Other hemoglobin variant carrier</td>
<td>Generally asymptomatic</td>
</tr>
</tbody>
</table>

Diagnosis:
Screening for sickle cell disease and other hemoglobinopathies is done using dried-blood-spot screening
tests. All first filter paper samples are screened for hemoglobinopathies using Isoelectric Focusing (IEF).
Various hemoglobin patterns occur. If an abnormality is detected, the sample is reanalyzed using high
performance liquid chromatography (HPLC). No fresh sample is requested for confirmation.

Monitoring:
Monitor patients with sickle cell trait who are exposed to reduced levels of oxygen (excessive exercise or
high altitudes) for blood in the urine, pain or difficulty breathing. No monitoring is necessary for other
hemoglobin traits.
Treatment:
No treatment.

Illness and Immunizations:
Immunizations should be kept current.

Growth and Development:
Monitor child for normal growth and developmental milestones.

The information provided is offered for general information and educational purposes only. It is not offered as and does not constitute medical advice. In no way are any of the materials presented meant to be a substitute for professional medical care or attention by a qualified practitioner, nor should they be construed as such.

November 2005
Section 5.
Cystic Fibrosis
Cystic Fibrosis Consultants

The following healthcare providers serve as consultants to Virginia Newborn Screening Services.

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Fact Sheet: Cystic Fibrosis

The following fact sheet is intended to provide healthcare providers with an overview of cystic fibrosis, which is a required screening effective March 1, 2006.

- Cystic Fibrosis
Cystic Fibrosis (CF)

Description:
Cystic Fibrosis (CF) is an autosomal recessive disorder. CF is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) protein, a complex chloride channel found in all exocrine tissues. CFTR controls the flow of water and certain salts in and out of the body's cells. As the movement of salt and water in and out of cells is altered, mucus becomes thickened. The thickened mucus can affect many organs and body systems including the lungs, sinuses, pancreas, liver, intestine, and reproductive tract, and to increased salt content in sweat gland secretions. This was considered a childhood disease in the past with the median survival age of 8. As of 2005, the median age is approximately 35.

General Population Incidence:
CF occurs most commonly in Caucasians, in about 1 in 2,500 Caucasian live births. CF occurs in about 1 in 8,500 for Hispanics, 1 in 15,000 for African Americans, and 1 in 31,000 for Asians. CF has also been reported in other ethnic groups, including Native American, Middle East, and Pacific Islander populations.

Symptoms:
- Chronic diarrhea
- Poor growth/ failure to thrive
- Foul-smelling stools
- Meconium ileus
- Rectal prolapse
- Abdominal pain
- Chronic pancreatitis
- Frequent episodes of wheezing
- Persistent cough
- Recurrent pneumonia
- Salty-tasting skin
- Chronic sinus infection
- Nasal polyps

Newborn Screening Technology:
CF is detected by an immunoflourescent assay (IFA) technique for Immununoreceative trypsinogen (IRT). IFA first measures the level of IRT in the blood. For infants whose IRT is either the highest 5% of results or above 60 ng/ml, the test result is confirmed by repeat testing. The interpretation of generated IRT result is then based on the infant’s age. If meconium ileus is present, then the IRT could show a false normal result.

Diagnosis:
Diagnosis is based upon compatible clinical findings with biochemical or genetic confirmation. The laboratory evidence for CFTR dysfunction includes either a sweat chloride above 60 mEq/L for two tests, identification of two CF mutations, or an abnormal nasal potential difference measurement. Compatible clinical findings include presence of typical clinical features, a history of CF in a sibling, or a positive newborn screening test. It is important to note that normal sweat chloride does not absolutely rule out CF. An important fact is that 10% to 15% of patients with Cystic Fibrosis are pancreatic sufficient.
Treatment:

- Regular outpatient monitoring with a multi-disciplinary team including physician, nurses, dieticians, respiratory therapists, social workers, and school health personnel (e.g., school nurses), at least every 3 months, preferably by a Cystic Fibrosis Center
- Management of problems that cause lung obstruction, which may involve:
  - Chest physical therapy (to help loosen and clear lung secretions; this may include manual hand therapy, a therapy vest, and devices such as a percussor or flutter, which vibrate the chest wall and loosen secretions).
  - Exercise (to loosen mucus, stimulate coughing, and improve overall physical condition).
  - Medications (to thin, reduce mucus and help breathing, such as Deoxyribonuclease, bronchodilators, and anti-inflammatory medications).
  - Antibiotics (to treat infections).
- Management of digestive and weight problems, which may involve:
  - Appropriate diet.
  - Pancreatic enzymes to aid digestion.
  - Vitamin supplements.
  - Treatments for intestinal obstructions.
- Psychosocial support (dealing with issues such as independence, sterility and sexuality, financial issues, and relationships).

Immunizations:
Immunization schedules should be followed to ensure protection from all other childhood diseases. It is crucial that patients with Cystic Fibrosis receive the Influenza vaccine each year.

Growth and development:
It is crucial to monitor all growth parameters on a regular basis.

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November 2005
Section 6.
Newborn Screening
Frequently Asked Questions
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What diseases in addition to phenylketonuria (PKU) are screened by Virginia Newborn Screening Services? Is the testing mandated?

The *Code of Virginia*, Section 32.1-65, mandates that every infant born in Virginia shall be subjected to screening tests for various disorders consistent with, but not necessarily identical to, the uniform condition panel recommended by the American College of Medical Genetics in its report *Newborn Screening: Toward a Uniform Screening Panel and System*.

Who is responsible for processing newborn screening samples in Virginia?

Currently, the Virginia Department of General Services, Division of Consolidated Laboratory Services, Newborn Screening Section (“Newborn Screening Laboratory”), is responsible for testing all infant samples in Virginia.

How long does the screening process take?

Currently, it takes the Newborn Screening Laboratory approximately 3 days to process and complete the screening on a routine sample. When additional testing is required, the screening time may be lengthened.

When should the newborn screening sample be collected?

According to the Newborn Screening Regulations (12 VAC 5-71), an infant must be equal to or older than 24 hours of age in order to obtain a satisfactory sample for screening. Prior to this time, enzyme and amino acid levels may be inadequate and could result in false negative test results. The sample should be taken prior to transfusing blood or blood products regardless of the infant’s age at the time of collection.

What is the cut-off age for an infant when accepting samples for newborn screening?

Samples are accepted from birth to 6 months of age. Samples taken from children over 6 months of age are considered unsatisfactory for newborn screening filter paper analysis. The test methodologies employed are set for hematocrit levels \( \geq 60\% \). Any changes in blood saturation, such as those that normally occur with the aging of the infant, may render the test invalid.

What is the difference between confirmation testing and diagnostic testing?

**Confirmation testing** refers to the screening procedures performed on a second or repeat sample to affirm the results of the initial test. The Newborn Screening Laboratory performs confirmatory tests.

**Diagnostic testing** refers to identification of a disease state or condition utilizing the confirmatory process but also involving other more specialized and specific testing methodologies. Diagnostic testing typically does not take place at the Newborn Screening Laboratory.
Does the Virginia Department of General Services, Division of Consolidated Laboratory Services perform diagnostic studies?

The Newborn Screening Laboratory does not perform diagnostic studies.

What is the difference between an abnormal value and a critical value?

An abnormal value is any test result that falls outside the normal range for that test methodology as established by the Newborn Screening Laboratory.

A critical value is an abnormal test result that may be highly indicative of a disease process and warrants immediate notification to the infant’s primary health care provider and the medical consultants by Newborn Screening Nurses, Virginia Department of Health.

What is Tandem Mass Spectrometry?

Tandem mass spectrometry (MS/MS) technology enables improvements in and consolidation of metabolic screening methods to detect amino acid disorders (e.g., PKU, maple syrup urine disease, and homocystinuria) among newborns, and does so with a relatively low false-positive rate. MS/MS technology expands the metabolic disorder screening panel (i.e., the number of disorders that can be detected) by incorporating an acylcarnitine profile, which enables detection of fatty acid oxidation disorders (e.g., medium-chain acyl-CoA dehydrogenase [MCAD] deficiency) and other organic acid disorders. 4

Will I be notified of my patients’ newborn screening results?

Results are mailed back to the submitter (usually the hospital of birth) and the primary health care provider listed on the filter paper device for all newborn-screening tests. In addition, the health care provider/physician listed on the filter paper device is also notified by telephone within 24 hours regarding all critically abnormal results by either the Newborn Screening Nurses at the Division of Child and Adolescent Health, Virginia Department of Health or by the Newborn Screening Section at the Division of Consolidated Laboratory Services, Virginia Department of General Services (depending on the presumptive disease).

Whom should I contact for interpretation of laboratory results and for follow-up consultation?

Questions concerning the interpretation of results should be directed to the Virginia Department of General Services, Division of Consolidated Laboratory Services, Newborn Screening Section, 600 North 5th Street, Richmond, VA 23219, telephone (804) 648-4480.

Questions regarding follow-up procedures should be directed to Virginia Department of Health, Virginia Newborn Screening Services, 109 Governor Street, 8th Floor, Richmond, VA 23219, telephone (804) 864-7714, 7715, or 7729.

Is professional medical assistance available if I have an infant with an abnormal result or have questions related to diagnostic testing or treatment protocols?

The Virginia Department of Health has established relationships with metabolic, endocrine and cystic fibrosis consultants to provide assistance with test interpretation, diagnostic testing, and treatment of affected infants. It is strongly recommended that these specialists be consulted to ensure the best outcome for affected or potentially affected infants.

When is a second newborn screening needed?

The second screen is required WHEN AN ABNORMAL TEST RESULT OCCURS or when a sample has been collected when the infant is less than 24 hours of age. When this happens, the submitter (usually the hospital of birth) and the health care provider listed on the filter paper device are notified in writing by the Virginia Department of General Services, Division of Consolidated Laboratory Services, Newborn Screening Section. In cases when a requested repeat specimen is not received by the Division of Consolidated Laboratory Services by 20 work days from the time the initial specimen was received, the Newborn Screening Nurses, Virginia Department of Health, place a follow-up call or sends a letter to the submitter or the health care provider listed on the filter paper device requesting submittal of the specimen as soon as possible.

What factors may affect the outcome of the newborn screening tests?

1. Heat
2. Transfusions
3. Foreign substances (e.g., body or tissue fluids, water, detergent, diet, soda, powder from latex gloves, and so forth).

How long should the provider wait to rescreen an infant who has been transfused?

Given the 120-day lifespan of the normal, healthy red blood cell and the presumption that the mean age of red blood cells of the transfused blood is 60-80 days, it is suggested that a sample be collected 60 days post transfusion.

Does acidosis (i.e., metabolic acidosis) affect the newborn screening test?

Metabolic acidosis does not appear to affect the results of the newborn screening test.

Does hypoglycemia affect the outcome of the newborn screening test?

Hypoglycemia in the sick newborn generally should not affect the screening results.

Does total parenteral nutrition (TPN) affect the outcome of the newborn screening test?

If the infant received total parental nutrition prior to sample collection it may cause false positive results for metabolic disorders.

Do I have to pay for the repeat sample?

Effective November 1, 2005, the charge for all Newborn Screening (NBS) services provided by the Division of Consolidated Laboratories Services and the Virginia Department of Health is $53.00 per infant. The NBS fee includes the initial collection card and any additional collection cards requested.
on that infant. The additional collection cards will be provided to the physician of record, enclosed with the report of abnormal results, for no additional fee. This includes requests to confirm initial abnormal test results as well as for any other reason such as specimen collected before the infant is 24 hours of age or unsatisfactory specimens. The only additional collection cards that a health care provider would have to purchase would be cards that the provider wishes to have on hand for unsolicited NBS sample collection.

**What is the procedure for placing an order for the newborn screening filter paper devices?**

Order forms may be obtained by calling the Virginia Department of General Services, Division of Consolidated Laboratories at (804) 648-4480, Ext. 103. The forms are to be completed and returned, together with a check for the amount of the purchase, to the Virginia Department of General Services, Office of Fiscal Services. Kit orders are processed upon receipt of the prepaid offer. Devices can also be ordered by phone when a credit card is used.

**Can my patient be referred to the local health department if repeat testing is required? Is there a cost involved?**

There is no cost involved when a repeat test is required by Virginia Newborn Screening Services—a second filter paper card will accompany the abnormal results. If a serum test is requested, the responsibility rests with the primary care physician and/or patient’s parent or guardian to make financial arrangements for direct or third party payment to the laboratory performing the testing. Referral to the local health department is not recommended.

**How can a copy of the infant’s newborn screening results be obtained?**

To get a copy of newborn screening results, write to:

Virginia Department of General Services  
Division of Consolidated Laboratories  
600 North 5th Street  
Richmond, VA 23219  
ATTN: Newborn Screening Laboratory  
Phone: (804) 648-4480  FAX: (804) 225-2595

Please provide information regarding the infant’s name, date of birth, mother’s name, mother’s social security number, hospital of birth, and sample number if known to assist in identifying the appropriate records.

**How can a copy of the current Newborn Screening law be obtained?**

The Newborn Screening law is available for download from the following Web site:

- **Code of Virginia**: [http://leg1.state.va.us/000/src.htm](http://leg1.state.va.us/000/src.htm). The applicable Code of Virginia sections are §§ 32.1-65 through 32.1-67.1.

- **Note**: An Act to amend and reenact §§ 32.1-65 through 32.1-67.1 of the Code of Virginia and to repeal the second enactment of Chapter 440 of the 2002 Acts of Assembly, relating to newborn screening services, approved March 25, 2005, is available online at [http://leg1.state.va.us/cgi-bin/legp504.exe?051+ful+CHAP0721](http://leg1.state.va.us/cgi-bin/legp504.exe?051+ful+CHAP0721).
How can a copy of the current Newborn Screening Rules and Regulations be obtained?

The Newborn Screening Regulations are available for download from the following Web sites:

  
  Navigate your browser to Virginia General Assembly, Legislative Information System, Virginia Administrative Code, Agency 5 – Department of Health, Chapter 70.
  
  Note: Effective March 1, 2006, Emergency Regulations will replace the above regulations.

  
  Navigate your browser to: Virginia Regulatory Town Hall, Secretariat: Health and Human Resources, Agency: Department of Health, Board: State Board of Health, Code Citation 12 VAC 5-70, Regulations Governing the Newborn Screening and Treatment Program.
  
  Note: Effective March 1, 2006, Emergency Regulations will replace the above regulations.
  Navigate your browser to: Virginia Regulatory Town Hall, Secretariat: Health and Human Resources, Agency: Department of Health, Board: State Board of Health, Code Citation 12 VAC 5-71, Regulations Governing Virginia Newborn Screening Services.

How does a child get referred to Care Connection for Children?

Confirmed diagnosis of newborn screened disorders are reported to Virginia Newborn Screening Services (VNSS) nurses by primary care providers and/or metabolic consultants. After the diagnosis is received, VNSS nurses will initiate a referral to the CCC site closest to the child’s residence. CCC staff will then initiate contact with the family to determine service needs.

Note: Primary care providers may initiate referrals to CCC for children with special health care needs. Eligibility requirements are outlined below.

1. **Medical Eligibility**: Children with special health care needs eligible for CCC services are those who have disorders that:
   a. Have a physical basis;
   b. Have lasted, or are expected to last, at least 12 months; and
   c. Produce one of more of the following sequelae.
      (1) Need for health care and ancillary services over and above the usual for the child's age, or for special ongoing treatments, interventions, or accommodation at home or school.
      (2) Limitation in function, activities, or social role in comparison with healthy age peers in the general areas of physical, cognitive, emotional, and social growth and development.
      (3) Dependency on one of the following to compensate for, or minimize limitation of, function, activities, or social role: medications, special diet, medical technology, assistive devices or personal assistance.

2. **Age Eligibility**: Birth to 21 years of age.

3. **Residency Eligibility**: Virginia Resident

4. **Financial Eligibility** (required only for those seeking assistance from the CSHCN Pool of Funds):

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a. The CSHCN Pool of Funds provides a limited amount of money to assist CSHCN who are uninsured or underinsured whose families have gross family income at or below 300% of the Federal Poverty Level. The funds assist with payment of certain services such as medications, diagnostic testing, therapies, durable medical equipment, and hospitalizations.

b. Preauthorization is required for the use of CSHCN Pool of Funds.

Additional information about CCC is available from the following Web site: http://www.vahealth.org/specialchildren.

### What services does Care Connection for Children provide?

Care Connection for Children is a statewide network of Centers of Excellence for Children with Special Health Care Needs that serves persons from ages birth to 21 years who are diagnosed with a chronic physical disorder. Services provided for the children and their families include assistance in accessing specialty medical services and a medical home, care coordination, medical insurance benefits evaluation and coordination, information and referral, transition from child to adult oriented health care system, and family-to-family support.

The network is managed by the Virginia Department of Health. The location and contact information for the centers is available from the following Web site: http://www.vahealth.org/specialchildren

### Is any assistance available for the families to obtain metabolic formula, low protein modified food, and metabolic supplements for the treatment of the heritable disorders and genetic diseases identified through the Virginia Newborn Screening Services Program?

The Care Connection for Children centers manage a pool of funds for payment of certain services that are medically necessary for the treatment and monitoring of the child’s disorder, such as medications, metabolic formula, laboratory and imaging testing, durable medical equipment, therapies, and hospitalizations. To qualify, a family must meet financial eligibility requirements and have no other resources such as private or public insurance available.

The Office of Family Health Services, Virginia Department of Health, manages a Formula Distribution and Purchase Plan (FDPP) to provide certain metabolic formulas or mechanisms to purchase metabolic formula for individuals who meet the financial and medical eligibility criteria. It also manages a Food/Supplements Reimbursement Plan for low protein modified foods and metabolic supplements for individuals who meet the financial and medical eligibility criteria. Additional information is available from the following Web site: http://www.vahealth.org/childadolescenthealth

### What are “metabolic formulas”?

For the purposes of the VDH Formula Distribution and Purchase Plan, metabolic formulas means nutritional substances that are:

- Prescribed by a health professional with appropriate prescriptive authority;
- Specifically designed and formulated to be consumed or administered internally under the supervision of such health professional;
- Specifically designed, processed, or formulated to be distinct in one or more nutrients that are present in natural food; and
• Intended for the medical and nutritional management of patients with limited capacity to metabolize ordinary foodstuffs or limited capacity to metabolize certain nutrients contained in ordinary foodstuffs.

**What are “low protein modified foods” and “metabolic supplements?”**

For the purposes of the VDH Food/Supplements Reimbursement Plan:

- **Low protein modified foods** means foods that are specifically formulated to have less than one gram of protein per serving and intended to be used under the direction of a physician for the dietary treatment of inherited metabolic diseases.

- **Metabolic supplements** means certain dietary or nutritional substances that are intended to be used under the direction of a physician for the nutritional management of inherited metabolic diseases.

Note: For the purposes of the VDH Food/Supplements Reimbursement Plan, low protein modified foods and metabolic supplements do not include foods that are naturally low in protein and do not include metabolic formulas.
Disease-Specific Information and Confirmatory Testing

When a serum sample for hypothyroidism is required, where should the specimen be sent for testing?

Any serum sample for hypothyroidism should be sent to a hospital or private laboratory for testing.

Serum samples for other disorders may be requested for confirmation or diagnostics by the medical consultants. The medical consultant will provide specific information pertaining to collection and to which laboratory/agency it is to be sent.

NOTE: The Newborn Screening Section of the Division of Consolidated Laboratory Services serves as the Newborn Screening Laboratory and, therefore, does not process clinical samples for diagnostic studies.

What is FAV? Is this a sickle cell disorder? What is the treatment protocol?

FAV stands for Fetal Hgb-Adult-Hgb plus a Variant. There are 400+ structurally different hemoglobin types identified to date. The majority constitutes a single amino acid replacement in one of the globulin polypeptide chains. Most screening laboratories have the capability to identify seven to ten hemoglobin types. The remaining hemoglobin types are then designated as variants. Variants rarely cause problems or require repeat routine or specialized testing or treatments. Variant (“V”) IS NOT a type of hemoglobin. It is a term used to denote the remaining 400+ hemoglobins not specifically named by the lab apparatus. If there is a desire to identify the specific hemoglobin band, it is recommended that a specialized laboratory be contacted to determine precisely what type of blood specimen is required for the testing and, also, that the parents’ blood be analyzed to determine the source of the variation.

What is FAB?

FAB stands for Fetal Hgb-Adult Hgb-Barts Hgb. Hgb Barts normally disappears within 6 months of age. However, identifying Barts at birth can assist with identification of Alpha Thalassemia. If Hgb Barts is observed during newborn screening, it will be reported to the primary care provider. Follow up of Barts is left to the discretion of the primary care provider. No further testing is required by Virginia Newborn Screening Services.

Is Barts Hgb clinically significant?

Less than 5% Barts indicates that the baby may be a silent carrier of Alpha Thalassemia and should have no clinical problems. From 5% to 10% Barts indicates that the baby will probably have a mild anemia that will not be cured by taking iron. There should be no other clinical problems. More than 10% Barts indicates the need for further medical evaluation. The Division of Consolidated Laboratory Services screening/methodology does not provide results in percent. Some physicians order hemoglobin electrophoresis after 6 months of age to ensure that Barts has disappeared.

What is thalassemia? How does it differ from sickle cell disease?

Thalassemia is any one of a group of inherited autosomal recessive blood disorders in which there is failure in the synthesis of one of the globin chains, resulting in an anemic state and ineffective erythropoiesis. The typical thalassemia red blood cell has lower than normal amounts of Hgb A, is
microcytic, hypochronic, and may take a banana, sickle, or other configuration. The thalassemias occur more frequently in populations from countries bordering the Mediterranean, and Southeast Asia, India, and Southern Europe.

When a presumptive positive for thalassemia is received, it is recommended that a Quantitative Hgb A2 test be performed. The mean corpuscular volume (MCV) and the amount of A2 in the hemoglobin are needed in order to identify the type of thalassemia present.

NOTE: A persistently depressed Hgb with a normal erythrocyte protoporphyrin is often suggestive of Thalassemia Minor.

What are the screening and confirmatory tests for sickle cell disease?

The screening test for sickle cell disease uses an electrophoresis technique known as isoelectric focusing, which causes separation of the different hemoglobin bands. The bands are then compared to a control to determine their identity. The confirmatory test for hemoglobinopathies, High Pressure Liquid Chromatography (HPLC), gives the quantitative values and positively identifies the Hgb band.

Should Sickle-Dex be used to confirm the diagnosis of sickle cell disease?

SICKLE-DEX AND OTHER SOLUBILITY TESTS SHOULD NOT BE USED TO IDENTIFY SICKLE CELL DISEASE IN INFANTS. They lack sensitivity and specificity in the first few months of life. The amount of fetal Hgb in newborns can mask the S Hgb and give a false normal result. They lack the ability to identify Hgb C or SC Disease.
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Section 7.
Laboratory Test Methodologies
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Disease-Specific Testing Procedures

**Amino Acid Disorders**

**Phenylketonuria (PKU)**
- Phenylalanine level

**Homocystinuria (HCY)**
- Methionine level

**Maple Syrup Urine Disease (MSUD)**
- Leucine/Isoleucine level

**Citrullinemia (CIT)**
- Citrulline

**Argininosuccinic acidemia (ASA)**
- Citrulline

**Tyrosinemia Type I (TYR I)**
- Tyrosine

The technology used to test for the above disorders is tandem mass spectrometry (MS/MS). This testing produces ions from the compounds in the sample and analyzes the fragments according to mass/charge ratios. The quantities of amino acids are measured against internal standards for these substances.

**Organic Acid Disorders**

**Isovaleric acidemia (IVA)**
- C5 (Isovaleryl/2-Methyl-butyryl)

**Glutaric acidemia type I (GA I)**
- C5-DC (Glutaryl)

**Hydroxymethylglutaric aciduria or HMG-CoA lyase deficiency or 3-OH 3-CH3 glutaric aciduria (HMG)**
- C5-OH (3-Hydroxyisovaleryl)

**Multiple carboxylase deficiency (MCD)**
- Primary Marker: C3 (Propionyl)
- Secondary Marker: C5-OH (3-Hydroxyisovaleryl)

**Methylmalonic acidemia due to mutase deficiency (MUT)**
- Primary Marker: C3
- Secondary Markers: C4-DC (Methylmalonyl)
  C3/C2 ratio
Methylmalonic acidemia cblA and cblB forms (Cbl A,B)
- Primary Marker: C3
- Secondary Markers: C4-DC (Methylmalonyl)
  C3/C2 ratio

3-Methylcrotonyl-CoA carboxylase deficiency (3MCC)
- C5-OH (3-Hydroxyisovaleryl)

Propionic acidemia (PROP)
- Primary Marker: C3
- Secondary Marker: C3/C2 ratio

Beta-Ketothiolase deficiency (BKT):
- Primary Marker: C5:1 (Tiglyl/3-methylcrotonyl)
- Secondary Marker: C5-OH (3-Hydroxyisovaleryl)

The technology used to test for the above disorders is tandem mass spectrometry (MS/MS). This testing produces ions from the compounds in the sample and analyzes the fragments according to mass/charge ratios. The quantities of acylcarnitines are measured against internal standards for these substances.

**Fatty Acid Oxidation Disorders**

Medium-chain acyl-CoA dehydrogenase deficiency (MCAD)
- Primary Marker: C8 (Octanoyl)
- Secondary Markers: C6 (Hexanoyl)
  C10 (Decanoyl)
  C8/C10 ratio

Very long-chain acyl-CoA dehydrogenase deficiency (VLCAD)
- Primary Marker: C14:1 (Tetradecenoyl)
- Secondary Markers: C14 (Tetradecanoyl)
  C16 (Palmitoyl)

Long-chain 3-OH acyl-CoA dehydrogenase deficiency (LCHAD)
- Primary Marker: C16-OH (Hydroxy Palmitoyl)
- Secondary Markers: C16 (Palmitoyl)
  C18-1OH (Hydroxy Oleyl)

Trifunctional protein deficiency (TFP)
- C16-OH (Hydroxy Palmitoyl)

Carnitine uptake defect (CUD)
- C0 (Free carnitine)

The technology used to test for the above disorders is tandem mass spectrometry (MS/MS). This testing produces ions from the compounds in the sample and analyzes the fragments according to mass/charge ratios. The quantities of acylcarnitines are measured against internal standards for these substances.
Hemoglobinopathy Disorders

Sickle cell anemia (Hb SS)

Hb S/Beta-Thalassemia (Hb S/Th)

Hb S/C disease (Hb S/C)

Newborn hemoglobinopathies are screened using an electrophoresis technique known as isoelectric focusing. This procedure causes the separation of the different types of hemoglobin within a blood sample. Each abnormal hemoglobin band is read against a known control to determine its suspected identity.

The confirmation test procedure for hemoglobinopathies is performed on a High Pressure Liquid Chromatography (HPLC) that gives quantitative values and positive identification of the observed hemoglobin bands in the blood spot sample. This process allows for a final screening result using a filter paper sample, thereby eliminating a requirement for a whole blood sample.

Other Disorders

Galactosemia (GALT)

The test procedure for galactosemia is the Beutler test, which is a biochemical assay detecting galactose-1-phosphate uridyl transferase enzyme. Specimens that demonstrate decreased fluorescence on the Beutler test receive the Hill test to quantitate the amount of galactose as well as galactose-one-phosphate present in the blood.

Biotinidase (BIOT)

Biotinidase deficiency is detected by a colorimetric test procedure. After incubation and development, a purple color indicates the presence of adequate biotinidase enzyme activity. The absence of color indicates very low biotinidase enzyme activity.

Congenital hypothyroidism (CH)

Congenital hypothyroidism is detected by an immunofluorescent assay (IFA) for thyroxine (T4) and thyroid stimulating hormone (TSH). IFA first measures the level of T4 in the blood. For infants whose T4 level falls in the lowest 10% of the results for the assay, TSH is measured on the same specimen.

Congenital adrenal hyperplasia (CAH)

CAH is detected by an immunofluorescent assay (IFA) for 17-hydroxy progesterone (17-OHP). IFA first measures the level of 17-OHP in the blood. For infants whose 17-OHP is either the highest 3% of results or above 40 ng/mL, the test result is confirmed by repeat testing. The interpretation of the generated 17-OHP result is then based on the infant’s birth weight.

Cystic fibrosis (CF)

CF is detected by an immunofluorescent assay (IFA) for Immunoactive trypsinogen (IRT). IFA first measures the level of IRT in the blood. For infants whose IRT is either the highest 5% of results or above 60 ng/mL, the test result is confirmed by repeat testing. The interpretation of the generated IRT result is then based on the infant’s age.
Appendices
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Appendix A.
Normal, Abnormal, and Critical Laboratory Test Values

Virginia Newborn Screening Laboratory
Division of Consolidated Laboratory Services
Virginia Department of General Services

<table>
<thead>
<tr>
<th>Part 1. Normal Ranges (Within Normal Limits)</th>
</tr>
</thead>
</table>

### Amino Acid Disorders

**Phenylketonuria (PKU)**
- Phenylalanine level < 140 µmol/l

**Homocystinuria (HCY)**
- Methionine level < 70 µmol/l

**Maple Syrup Urine Disease (MSUD)**
- Leucine/Isoleucine < 310 µmol/l

**Citrullinemia (CIT)**
- Citrulline < 75 µmol/l

**Argininosuccinic acidemia (ASA)**
- Citrulline < 75 µmol/l

**Tyrosinemia Type I (TYR I)**
- Tyrosine < 442 µmol/l

### Organic Acid Disorders

**Isovaleric acidemia (IVA)**
- C5 (Isovaleryl/2-Methyl-butyryl) < 0.87 µmol/l

**Glutaric acidemia type I (GA I)**
- C5-DC (Glutaryl) < 0.30 µmol/l
- Hydroxymethylglutaric aciduria or HMG-CoA lyase deficiency or 3-OH 3-CH3 glutaric aciduria (HMG):
  - C5-OH (3-Hydroxyisovaleryl) < 1.0 µmol/l

**Multiple carboxylase deficiency (MCD)**
- Primary Marker: C3 (Propionyl) < 6.0 µmol/l
- Secondary Marker: C5-OH (3-Hydroxyisovaleryl) < 1.0 µmol/l
Methylmalonic acidemia due to mutase deficiency (MUT)
- Primary Marker: C3 < 6.0 µmol/l
- Secondary Markers: C4-DC (Methylmalonyl) < 1.0 µmol/l
  C3/C2 ratio < 0.32

Methylmalonic acidemia cblA and cblB forms (Cbl A,B)
- Primary Marker: C3 < 6.0 µmol/l
- Secondary Markers: C4-DC (Methylmalonyl) < 1.0 µmol/l
  C3/C2 ratio < 0.32

3-Methylcrotonyl-CoA carboxylase deficiency (3MCC)
- C5-OH (3-Hydroxyisovaleryl) < 1.0 µmol/l

Propionic acidemia (PROP)
- Primary Marker: C3 < 6.0 µmol/l
- Secondary Marker: C3/C2 ratio < 0.32

Beta-Ketothiolase deficiency (BKT)
- Primary Marker: C5:1 (Tiglyl/3-methylcrotonyl) < 0.33 µmol/l
- Secondary Marker: C5-OH (3-Hydroxyisovaleryl) < 1.0 µmol/l

Fatty Acid Oxidation Disorders

Medium-chain acyl-CoA dehydrogenase deficiency (MCAD)
- Primary Marker: C8 (Octanoyl) < 0.50 µmol/l
- Secondary Markers: C6 (Hexanoyl) < 0.59 µmol/l
  C10 (Decanoyl) < 0.55 µmol/l
  C8/C10 ratio < 3.0

Very long-chain acyl-CoA dehydrogenase deficiency (VLCAD)
- Primary Marker: C14:1 (Tetradecenoyl) < 0.66 µmol/l
- Secondary Markers: C14 (Tetradecanoyl) < 0.70 µmol/l
  C16 (Palmitoyl) < 7.79 µmol/l

Long-chain 3-OH acyl-CoA dehydrogenase deficiency (LCHAD)
- Primary Marker: C16-OH (Hydroxy Palmitoyl) < 0.10 µmol/l
- Secondary Markers: C16 (Palmitoyl) < 7.79 µmol/l
  C18-1OH (Hydroxy Oleyl) < 0.11 µmol/l

Trifunctional protein deficiency (TFP)
- C16-OH (Hydroxy Palmitoyl) < 0.10 µmol/l

Carnitine uptake defect (CUD)
- C0 (Free carnitine) > 7.0 µmol/l

Hemoglobinopathy Disorders
(F/A) Fetal and adult hemoglobin present with fetal hemoglobin in predominance.
(A/F) Adult hemoglobin present in slightly higher quantity than fetal hemoglobin for an infant who has not been transfused. (Seen commonly in infants 2 months of age or older.)
Other Disorders

**Galactosemia (GALT)**
- Beutler – Enzyme activity present
- Hill: < 10mg/dl

**Biotinidase (BIOT)**
- Enzyme activity present

**Congenital hypothyroidism (CH):**
- T4: > 5.5 mcg/dL.
- TSH: < 24.0 μU/ml

**Congenital adrenal hyperplasia (CAH):**

<table>
<thead>
<tr>
<th>Birth weight category</th>
<th>Normal 17-OHP (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1250 gms</td>
<td>&lt;135</td>
</tr>
<tr>
<td>1250 – 1749 gms</td>
<td>&lt;90</td>
</tr>
<tr>
<td>1750 – 2249 gms</td>
<td>&lt;65</td>
</tr>
<tr>
<td>≥2250 gms</td>
<td>&lt;50</td>
</tr>
</tbody>
</table>

**Cystic fibrosis (CF):**
- Immunoreactive trypsinogen (IRT): < 90 ng/ml for < 21 days of age
  < 70 ng/ml for > 21 days of age

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**Part 2. Abnormal Ranges**

**Amino Acid Disorders**

**Phenylketonuria (PKU)**
- Phenylalanine level ≥ 140 to < 280 μmol/l

**Homocystinuria (HCY)**
- Methionine level ≥ 70 to < 140 μmol/l

**Maple Syrup Urine Disease (MSUD)**
- Leucine/Isoleucine ≥ 310 to < 460 μmol/l

**Citrullinemia (CIT)**
- Citrulline ≥ 75 to < 100 μmol/l

**Argininosuccinic acidemia (ASA)**
- Citrulline ≥ 75 to < 100 μmol/l

**Tyrosinemia Type I (TYR I)**
- Tyrosine ≥ 442 to < 500 μmol/l
Organic Acid Disorders

Isovaleric acidemia (IVA)
- C5 (Isovaleryl/2-Methyl-butyryl) ≥ 0.87 to < 1.62 µmol/l

Glutaric acidemia type I (GA I)
- C5-DC (Glutaryl) ≥ 0.30 µmol/l

Hydroxymethylglutaric aciduria or HMG-CoA lyase deficiency or 3-OH 3-CH3 glutaric aciduria (HMG)
- C5-OH (3-Hydroxyisovaleryl) ≥ 1.0 to < 2.0 µmol/l

Multiple carboxylase deficiency (MCD)
- Primary Marker: C3 (Propionyl) ≥ 6.0 to < 8.0 µmol/l
- Secondary Marker: C5-OH (3-Hydroxyisovaleryl) ≥ 1.0 to < 2.0 µmol/l

Methylmalonic acidemia due to mutase deficiency (MUT)
- Primary Marker: C3 ≥ 6.0 to < 8.0 µmol/l
- Secondary Markers: C4-DC (Methylmalonyl) ≥ 1.0 to < 1.5 µmol/l
  C3/C2 ratio ≥ 0.32

Methylmalonic acidemia cblA and cblB forms (Cbl A,B)
- Primary Marker: C3 ≥ 6.0 to < 8.0 µmol/l
- Secondary Markers: C4-DC (Methylmalonyl) ≥ 1.0 to < 1.5 µmol/l
  C3/C2 ratio ≥ 0.32

3-Methylcrotonyl-CoA carboxylase deficiency (3MCC)
- C5-OH (3-Hydroxyisovaleryl) ≥ 1.0 to < 2.0 µmol/l

Propionic acidemia (PROP)
- Primary Marker: C3 ≥ 6.0 to < 8.0 µmol/l
- Secondary Marker: C3/C2 ratio ≥ 0.32

Beta-Ketothiolase deficiency (BKT)
- Primary Marker: C5:1 (Tiglyl/3-methylcrotonyl) ≥ 0.33 to < 1.0 µmol/l
- Secondary Marker: C5-OH (3-Hydroxyisovaleryl) ≥ 1.0 to < 2.0 µmol/l

Fatty Acid Oxidation Disorders

Medium-chain acyl-CoA dehydrogenase deficiency (MCAD)
- Secondary Markers: C6 (Hexanoyl) ≥ 0.59 to < 1.0 µmol/l
  C10 (Decanoyl) ≥ 0.55 to < 0.9 µmol/l
  C8/C10 ratio ≥ 3.0

Very long-chain acyl-CoA dehydrogenase deficiency (VLCAD)
- Primary Marker: C14:1 (Tetradecenoyl) ≥ 0.66 to < 1.5 µmol/l
- Secondary Markers: C14 (Tetradecanoyl) ≥ 0.70 to < 0.92 µmol/l
  C16 (Palmitoyl) ≥ 7.79 to < 10.8 µmol/l
**Long-chain 3-OH acyl-CoA dehydrogenase deficiency (LCHAD)**
- **Primary Marker:** C16-OH (Hydroxy Palmitoyl) ≥ 0.10 to < 0.19 µmol/l
- **Secondary Markers:** C16 (Palmitoyl) ≥ 7.9 to < 10.8 µmol/l  
  C18-1OH (Hydroxy Oleyl) ≥ 0.11 to < 0.5 µmol/l

**Trifunctional protein deficiency (TFP)**
- C16-OH (Hydroxy Palmitoyl) ≥ 0.10 to < 0.19 µmol/l

**Carnitine uptake defect (CUD)**
- C0 (Free carnitine) ≤ 7.0 to > 3.0 µmol/l

**Hemoglobinopathy Disorders**

**Sickle Cell Disease (Hb SS, SC, SD, SE, SV)**
- Hemoglobin Traits – F/A/S, F/A/C, F/A/D, F/A/E, or FAB
- (A/F) Adult hemoglobin present in higher quantity than fetal hemoglobin in an infant who has been transfused.
- (F/A/V) Where “V” indicates the presence of an identified hemoglobin variant.

**Other Disorders**

**Galactosemia (GALT)**
- Beutler abnormal (no enzyme activity)  
  Hill 10 -14 mg/dl  
- Beutler within normal limits  
  Hill 10 – 14 mg/dl

**Biotinidase (BIOT)**
- Partial to no enzyme activity.

**Congenital hypothyroidism (CH)**
- T4: < 5.5 mcg/dL
- TSH: ≥ 24.0 to 59.0 µU/ml

**Congenital adrenal hyperplasia (CAH)**

<table>
<thead>
<tr>
<th>Birth weight category</th>
<th>Normal 17-OHP (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1250 gms</td>
<td>135 - 159</td>
</tr>
<tr>
<td>1250 – 1749 gms</td>
<td>90 – 134</td>
</tr>
<tr>
<td>1750 – 2249 gms</td>
<td>65 – 89</td>
</tr>
<tr>
<td>≥2250 gms</td>
<td>50 - 89</td>
</tr>
</tbody>
</table>

**Cystic fibrosis (CF)**
- Immunoreactive trypsinogen (IRT): ≥ 90 ng/ml for < 21 days of age  
  ≥ 70 ng/ml for > 21 days of age
Amino Acid Disorders

**Phenylketonuria (PKU)**
- Phenylalanine level $\geq 280$ µmol/l

**Homocystinuria (HCY)**
- Methionine level $\geq 140$ µmol/l

**Maple Syrup Urine Disease (MSUD)**
- Leucine/Isoleucine $\geq 460$ µmol/l

**Citrullinemia (CIT)**
- Citrulline $\geq 100$ µmol/l

**Argininosuccinic acidemia (ASA)**
- Citrulline $\geq 100$ µmol/l

**Tyrosinemia Type I (TYR I)**
- Tyrosine $\geq 500$ µmol/l

Organic Acid Disorders

**Isovaleric acidemia (IVA)**
- C5 (Isovaleryl/2-Methyl-butryl) $\geq 1.62$ µmol/l

**Glutaric acidemia type I (GA I)**
- C5-DC (Glutaryl) $\geq 0.30$ µmol/l

**Hydroxymethylglutaric aciduria or HMG-CoA lyase deficiency or 3-OH 3-CH3 glutaric aciduria (HMG)**
- C5-OH (3-Hydroxyisovaleryl) $\geq 2.0$ µmol/l

**Multiple carboxylase deficiency (MCD)**
- Primary Marker: C3 (Propionyl) $\geq 8.0$ µmol/l
- Secondary Marker: C5-OH (3-Hydroxyisovaleryl) $\geq 2.0$ µmol/l
- 2 or more abnormal results of C3, C5-OH

**Methylmalonic acidemia due to mutase deficiency (MUT)**
- Primary Marker: C3 $\geq 8.0$ µmol/l
- Secondary Marker: C4-DC (Methylmalonyl) $\geq 1.50$ µmol/l
- 2 or more abnormal results of C3, C4-DC, C3/C2 ratio
Methylmalonic acidemia cblA and cblB forms (Cbl A,B)
• Primary Marker: C3 ≥ 8.0 µmol/l
• Secondary Marker: C4-DC (Methylmalonyl) ≥ 1.50 µmol/l
• 2 or more abnormal results of C3, C4-DC, C3/C2 ratio

3-Methylcrotonyl-CoA carboxylase deficiency (3MCC)
• C5-OH (3-Hydroxyisovaleryl) ≥ 2.0 µmol/l

Propionic acidemia (PROP)
• Primary Marker: C3 ≥ 8.0 µmol/l
• 2 or more abnormal results of C3, C3/C2 ratio

Beta-Ketothiolase deficiency (BKT)
• Primary Marker: C5:1 (Tiglyl/3-methylcrotonyl) ≥ 1.0 µmol/l
• Secondary Marker: C5-OH (3-Hydroxyisovaleryl) ≥ 2.0 µmol/l
• 2 or more abnormal results of C5:1, C5-OH

Fatty Acid Oxidation Disorders:

Medium-chain acyl-CoA dehydrogenase deficiency (MCAD)
• Primary Marker: C8 (Octanoyl) ≥ 1.0 µmol/l
• Secondary Markers: C6 (Hexanoyl) ≥ 1.0 µmol/l
  C10 (Decanoyl) ≥ 0.9 µmol/l
• 2 or more abnormal results of C6, C8, C10, C8/C10 ratio

Very long-chain acyl-CoA dehydrogenase deficiency (VLCAD)
• Primary Marker: C14:1 (Tetradecenoyl) ≥ 1.5 µmol/l
• Secondary Markers: C14 (Tetradecanoyl) ≥ 0.92 µmol/l
  C16 (Palmitoyl) ≥ 10.8 µmol/l
• 2 or more abnormal results of C14, C14:1, C16

Long-chain 3-OH acyl-CoA dehydrogenase deficiency (LCHAD)
• Primary Marker: C16-OH (Hydroxy Palmitoyl) ≥ 0.19 µmol/l
• Secondary Markers: C16 (Palmitoyl) ≥ 10.8 µmol/l
  C18-1OH (Hydroxy Oleyl) ≥ 0.5 µmol/l
• 2 or more abnormal results of C16, C16-OH, C18-1OH

Trifunctional protein deficiency (TFP)
• C16-OH (Hydroxy Palmitoyl) ≥ 0.19 µmol/l

Carnitine uptake defect (CUD)
• C0 (Free carnitine) ≤ 3.0 µmol/l

Hemoglobinopathy Disorders

Sickle Cell Disease
• Sickle Cell Disease (F/S)
• SC Disease (F/S/C)
• SE Disease (F/S/E)
• SD Disease (F/S/D)
• Sickle Beta+ Thalassemia (F/S/A)

Other Hemoglobinopathies
• C Disease (F/C)
• FCA C Beta+ Thalassemia
• FE Disease (F/E)
• FEA E Beta+ Thalassemia
• FV Unknown Variant
• F Hemoglobin only (possible Cooley’s Anemia)

Other Disorders

Galactosemia (GALT)
• Beutler abnormal (no enzyme activity); Hill ≥ 15 mg/dl
• Beutler normal (enzyme activity); Hill ≥ 15 mg/dl
• Three consecutive samples with an abnormal Beutler

Biotinidase (BIOT)
• Two consecutive samples with abnormal results (partial or no enzyme activity)

Congenital hypothyroidism (CH)
• TSH: ≥ 60.0 µU/ml
• Two consecutive samples with abnormal T4

Congenital adrenal hyperplasia (CAH):

<table>
<thead>
<tr>
<th>Birth weight category</th>
<th>Normal 17-OHP (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1250 gms</td>
<td>≥ 160</td>
</tr>
<tr>
<td>1250 – 1749 gms</td>
<td>≥ 135</td>
</tr>
<tr>
<td>1750 – 2249 gms</td>
<td>≥ 90</td>
</tr>
<tr>
<td>≥2250 gms</td>
<td>≥ 90</td>
</tr>
</tbody>
</table>

Cystic fibrosis (CF)
• Immunoreactive trypsinogen (IRT) Two consecutive samples with abnormal results of: ≥ 90 ng/ml for < 21 days of age
• ≥ 70 ng/ml for > 21 days of age
Appendix B.  
Unsatisfactory Specimen Criteria  

Virginia Newborn Screening Laboratory  
Division of Consolidated Laboratory Services  
Virginia Department of General Services  

Unsatisfactory  

The following unsatisfactory specimen criteria have been established in accordance with the standards provided by the National Committee for Clinical Laboratory Standards in regard to blood collection on filter paper for Neonatal Screening Programs (Document LA 4-A, Vol. 8 No. 9).  

Specimens are reported as unsatisfactory according to the following descriptions. Refer to the returned portion of the sample card to identify the appropriate UNSAT code number.  

Unsat Code Number  

1. Specimen unsat - improperly collected. Specimens that are not completely saturated when viewed from the reverse side or where the saturated blood does not completely fill the circle are quantity insufficient for testing.  

2. Specimen unsat - scratched or abraded. Specimen appears scratched, abraded, punctured, or indented due to applying blood with a capillary tube or other device.  

3. Specimen unsat - wet. Specimens that are wet or mailed prior to drying for a minimum of four hours.  

4. Specimen unsat - over saturated. Specimen appears streaked with blood clots, blood applied to both sides of filter paper, or layered with concentric circles of blood indicating multiple applications.  

5. Specimen unsat - contaminated. Specimen exhibits serum rings, or appears diluted, discolored, contaminated by antiseptic solution. Formulas, water, tissue fluids, or direct heat exposure.  

6. Specimen unsat - no blood. Filter spot is blank, failure to obtain blood specimen.  

7. Specimen unsat - insufficient information. Essential information for identification, categorization, interpretation and follow up were not provided. Essential information includes last name, submitter(s), birth date, mother's name and date of specimen collection.  

8. Specimen unsat - old sample > 10 days in transit. The integrity of the sample may be compromised on specimens received after more than 10 days in transit. Analyses such as enzymes measured in newborn screening are heat labile and may be adversely affected by exposure of specimens to hot and /or humid environments.  

9. Specimen unsat - infant > 6 months of age. Virginia newborn screening procedures and cut-off levels are based on the normal infant hematocrit. Samples from infants over six months of age are considered unsatisfactory for our screening procedures.
10. **Specimen unsat - outdated filter paper card.** Specimens collected on outdated filter paper cards may be compromised due to the unreliability of the filter paper. The age and condition of the filter paper directly affects the absorption of blood.

11. **Specimen unsat - insufficient quantity.** When testing has begun on a specimen and there is not enough specimen to complete each of the tests, some tests may be reported as unsatisfactory due to insufficient quantity.

12. **Specimen unsat - interfering substances present.** Valid results could not be obtained due to interfering substances, e.g., antibiotics, anticoagulants, etc.

13. **Specimen unsat - “other”.** This code number is reserved for any unsatisfactory specimen condition not appropriately described in codes 1-12. The Newborn Screening lab will provide comments to explain any unsatisfactory condition of this nature.

14. **Specimen unsat - parental refusal.** Hospital notification indicated that the baby’s parents refused newborn screening at time of discharge.

**Note:** Please obtain a valid specimen according to NCCLS guidelines, publication LA4-A “Blood Collection on Filter Paper for Neonatal Screening Programs.” Allow a sufficient quantity of blood to soak through to completely fill the pre-printed circles with blood. Do not layer successive drops of blood or apply blood more than once in the same collection circle. Avoid touching or smearing spots. For more information, please call the Virginia Newborn Screening Laboratory at (804) 648-4480.
Appendix C.
Proper Method for Collecting Neonatal Samples

Source: Schleicher & Schuell Bioscience, Inc.
Information provided by the New York State Department of Health.
http://www.schleicher-schuell.com/icm11be.nsf/(html)/FramesetBioScience
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1 Equipment: sterile lancet with tip approximately 2.0 mm, sterile alcohol prep, sterile gauze pads, soft cloth, blood collection form, gloves.

2 Complete ALL information. Do not contaminate filter paper circles by allowing the circles to come in contact with spillage or by touching before or after blood collection. Keep “SUBMITTER COPY” if applicable.

3 Hatched area indicates safe areas for puncture site.

4 Warm site with soft cloth, moistened with warm water up to 41°C, for three to five minutes.

5 Cleanse site with alcohol prep. Wipe DRY with sterile gauze pad.
6 Puncture heel. Wipe away first blood drop with sterile gauze pad. Allow another LARGE blood drop to form.

7 Lightly touch filter paper to LARGE blood drop. Allow blood to soak through and completely fill circle with SINGLE application to LARGE blood drop. (To enhance blood flow, VERY GENTLE intermittent pressure may be applied to area surrounding puncture site). Apply blood to one side of filter paper only.

8 Fill remaining circles in the same manner as step 7, with successive blood drops. If blood flow is diminished, repeat steps 5 through 7. Care of skin puncture site should be consistent with your institution's procedures.

9 Dry blood spots on a dry, clean, flat non-absorbent surface for a minimum of four hours.

10 Mail completed form to testing laboratory within 24 hours of collection.
Appendix D.
Improperly Collected Blood Spots and Their Cause

Source: Schleicher & Schuell Bioscience, Inc.
Information provided by the New York State Department of Health.
http://www.schleicher-schuell.com/icm11be.nsf/(html)/FramesetBioScience
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# Simple Spot Check

## Invalid Specimens:

1. **Specimen quantity insufficient for testing**

2. **Specimen appears scratched or abraded.**

3. **Specimen not dry before mailing.**

4. **Specimen appears supersaturated.**

5. **Specimen appears diluted, discolored or contaminated.**

6. **Specimen exhibits serum rings.**

7. **Specimen appears clotted or layered.**

8. **No blood.**

## Possible Causes:

- Removing filter paper before blood has completely filled circle or before blood has soaked through to second side.
- Applying blood to filter paper with a capillary tube.
- Touching filter paper before or after blood specimen collection with gloved or ungloved hands, hand lotion, etc.
- Allowing filter paper to come in contact with gloved or ungloved hands or substances such as hand lotion or powder, either before or after blood specimen collection.
- Applying blood with a capillary tube or other device.

- Mailing specimen before drying for a minimum of four hours.
- Applying excess blood to filter paper, usually with a device.
- Applying blood to both sides of filter paper.

- Squeezing or “milking” of area surrounding the puncture site.
- Allowing filter paper to come in contact with gloved or ungloved hands or substances such as alcohol, formula, antiseptic solutions, water, hand lotion or powder, etc., either before or after blood specimen collection.
- Exposing blood spots to direct heat.

- Not wiping alcohol from puncture site before making skin puncture.
- Allowing filter paper to come in contact with alcohol, hand lotion, etc.
- Squeezing area surrounding puncture site excessively.
- Drying specimen improperly.
- Applying blood to filter paper with a capillary tube.

- Touching the same circle on filter paper to blood drop several times.
- Filling circle on both sides of filter paper.

- Failure to obtain blood specimen.

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Information provided by The New York State Department of Health.
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