

New Mexico Practitioner's Manual



Northwest Regional Newborn Screening Program

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Children's Medical Services Newborn Screening Program**

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There have been great changes in newborn screening (NBS) programs in the last five to 10 years, both in terms of how NBS programs are viewed and the ability to screen for an increasing number of conditions.

Newborn screening is a public health system comprised of screening, follow-up, diagnosis, management, evaluation and education.¹ A systems approach recognizes the complexity and the multitude of stakeholders involved in NBS programs, including affected infants, children, adults, their families, practitioners, birthing facilities, mail and courier groups, treatment centers, schools, public health officials, legislators as well as the general public and the importance of effective communication between them. It also recognizes the great responsibility NBS programs have to identify affected infants in time to prevent damage and to ensure a seamless coordination of efforts of many people to that end. It is recognized that appropriate treatment must be available to every affected infant into adulthood and that long-term follow-up of the children is necessary regardless of geographic location. Finally, a systems approach emphasizes the importance of education and evaluation for everyone involved in NBS.

There is an **increasing number of conditions** for which NBS tests are now available. In the late 1990s, new technology, specifically tandem mass spectrometry (MS/MS), was adapted for use in NBS laboratories. It became possible to screen for more than 30 conditions from one small disc of blood. Previously, one bloodspot was needed for each separate test/condition and screening programs were limited as to the number of conditions that

could be included on the screening panel. Multiplex platforms, such as MS/MS and others under development, open the possibility of screening for hundreds of conditions. Once it is technically possible, we as a society must decide whether we should screen, and if so for what conditions.

Traditionally, screening programs in the United States have been administered and carried out by individual states' public health laboratories and/or health divisions. Screening panels and program amenities have been determined by the population risk for disorders and the resources available to each state. As a result, some states screened for as few as four disorders, while others screened for more than 30.² This disparity galvanized both public and private groups to demand more uniform and expanded screening panels and to ensure a "standard of care" for all infants in the United States. Most other countries have a national NBS program, rather than state/province driven programs.

Parents of children affected with conditions detectable through NBS have lobbied state and national legislatures to provide funding and authority for state screening programs to implement the new technology and expand the number of conditions included. There is increasing pressure from advocacy groups to screen for conditions that have unproven treatments or that do not meet the classical criteria outlined by the World Health Organization in the 1960s.³

In 2005 a report from the American College of Medical Genetics (ACMG), commissioned by the Maternal and Child Health Bureau of the Health Resources and Services Administration (HRSA),

recommended that all United States screening programs include a core panel of 29 conditions.² The National March of Dimes (MOD) organization not only supported the ACMG report, but began to issue "report cards" of state screening panels on their website.

Newborn screening is a public health system comprised of screening, follow-up, diagnosis, management, evaluation and education.

In 2003, the Secretary of Health and Human Services Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children (ACHDGDNC) was formed to provide guidance to reduce the morbidity and mortality from inherited disorders, particularly those identified through NBS. (www.hrsa.gov/heritabledisorderscommittee)

The Secretary's Committee has been effective in standardizing NBS policies and testing panels throughout the United States. In May 2010, the Committee recommended that severe combined immune deficiency (SCID) be added to the screening panels in the U.S.

In New Mexico on January 2005 it was enacted by the legislature of the State of New Mexico section 1. Section 24-1-6 nmsa 1978 (being laws 1973, chapter 359, section 6, as amended) "24-1-6. Tests required for newborn infants. To allow for the expanded newborn screening testing panel,

the Department of Health shall institute and carry on such laboratory services or may contract with another agency or entity to provide such services as are necessary to detect the presence of congenital diseases. The Oregon State Public Health Laboratory (OSPHL) has been awarded the competitive bid to provide the laboratory testing and tracking system.

While each of these conditions is rare, collectively they affect about one in 1,000 infants, so the chance that any single infant will be affected is remote. The cost of not detecting one of these conditions is immense, both in human suffering and financial terms, because early diagnosis and treatment can result in normal growth and development. Infants with these conditions appear normal at birth. It is only with time that the biochemical abnormality affects the infant's health and development.⁴

By the time clinical symptoms appear the damage may be permanent or the infant may die, sometimes without a diagnosis having been made. However, NBS is a screening test, not a diagnostic test, and not all affected infants will be identified even with two routine screening tests, as is recommended or mandated in the majority of our regional states.

The goal of the Northwest Regional Newborn Screening Program (NWRNSP), which includes Oregon, Idaho, Nevada, Alaska, Hawaii and New Mexico and military bases in California and Washington, is to identify as many affected infants as possible before damage can occur. To do so, every infant must be screened. This process

requires coordinated efforts from five groups of health care providers:

Practitioners: Responsible for collecting and handling screening specimens, for educating parents with correct and current information and for providing prompt follow-up in the event of an abnormal result.

Oregon State Public Health Laboratory (OSPHL) and follow-up team: Responsible for testing, record keeping, quality control of laboratory methods, notification of results and tracking of abnormal and unresolved results.

State Health Divisions and Oregon Health & Science University (OHSU) Subspecialty Programs: Responsible for ensuring confirmatory testing of infants with abnormal results, managing confirmed cases, collecting long term follow-up (LTFU) data and educating practitioners.

New Mexico's Newborn Screening Program and Subspecialty Programs at the University of New Mexico Health Science Center, Presbyterian Hospital and other subspecialty providers: Responsible for the management of confirmed cases, collection of long-term follow-up (LTFU) data and for education of practitioners.

New Mexico's Newborn Screening Program: New Mexico's screening program is responsible for State wide management of newborn screening, including program review, follow-up, tracking of results, assessment, and quality assurance, policy

development, educational brochures statewide trainings, monitoring of the contract with Oregon Public Health Laboratory and UPS courier service.

Practitioner's responsibilities to the program are termed Newborn Screening Practice (see [page 13-19](#)).⁵ A practitioner is defined as the person(s) responsible for supervising the birth and/or the early neonatal care of an infant. Inadequate screening practices can greatly affect the quality of screening tests and increase the chances that an affected infant may be missed or diagnosed late.

The OSPHL and the New Mexico Newborn Screening Program follow-up team, together with regional state health agencies, have developed a quality assurance program to assist practitioners in improving their screening practices. Components of this program include ongoing education for practitioners and parents, computerized monitoring of measurable screening practices, and an examination of communication channels between practitioners, the laboratory, the follow-up team and the treatment centers.

This manual describes the conditions currently covered by the program as well as the standards and common problems for certain screening practices, and provides general program information as well as bulleted "NBS Essentials" summaries at the beginning of each chapter. We invite practitioners to contact us with any questions or concerns that may arise.

10 important points to remember about NBS**1**

Please use the term “**Newborn Screening**” or “**Newborn Blood Spot Screening**”. The term, “**PKU test**” is outdated and confusing to parents. The screening panel now includes markers for approximately 30+ separate disorders, the most recently added being cystic fibrosis.

2

Incidence of all the blood spot conditions is now **one infant in 1000** or 45–50 new cases each year in Oregon (~1 infant/week identified).

3**Screen every normal infant TWICE**

- 1st screen: 24–48 hours of age or at discharge, whichever comes first
- 2nd screen: 10–14 days of age

4**Screen every NICU infant THREE TIMES**

- 1st: on admission (regardless of age)
- 2nd: 48-72 hours of age
- 3rd: 28 days of age or at discharge, whichever comes first

5**Validity of screening specimens:**

- 1st screen identifies 90% of all conditions (1st & 2nd for NICU)
- 2nd/3rd screen identifies 10% of all conditions

6**Goal of NBS- Diagnose and treat in the two weeks of life since:**

- ~ 20 disorders can kill or maim in the first week or two of life
- 10–20% of infants will be symptomatic in the first week
- 5–10% may die in the first week
- Infants with hypothyroidism and PKU lose significant IQ points if thyroid stimulating hormone (TSH) and phenylalanine are not under control by 2 weeks of age

7**Maintain high index of suspicion for early presentation of emergent conditions:**

- Symptoms: lethargy, poor feeding, weight loss or sudden cardiopulmonary arrest
- Five infants have died before 10 days of age in our region even with NBS. None of the diagnoses were suspected despite symptoms.
- 1–2% of affected infants may have false negative results
- Screening tests are not diagnostic and affected infants may be missed. Practitioners should remain alert for signs of these conditions in infants and children regardless of the screening result.

8**Primary blood markers in emergent conditions:**

- Hypoketotic **hypoglycemia**, sudden cardiopulmonary arrest (fatty acid oxidation disorders)
- **Hyperammonemia** (urea cycle disorders)
- **Acidosis** (organic acidemia)
- Abnormal **electrolytes** and **sodium** (congenital adrenal hyperplasia)
- **Reducing substances** in urine, liver dysfunction (galactosemia)

9**If parents refuse testing:**

- Complete Newborn Screening Test Refusal form and counsel parents (**page 33**)

10

Visit the New Mexico Department of Health or Oregon State Public Health Laboratory websites: www.health.state.nm/nbs or www.oregon.gov/DHS/ph/nbs/index.shtml

New Mexico newborns are screened for all core and secondary conditions recommended by the College of Medical Genetics and the March of Dimes.⁶ A description of these conditions start on page 33 and complete summaries are available on the OSPHL website:

www.oregon.gov/DHS/ph/nbs/index.shtm.

CYSTIC FIBROSIS*

ENDOCRINE CONDITIONS:

- Congenital adrenal hyperplasia (CAH)*±
- Congenital hypothyroidism*

HEMOGLOBIN CONDITIONS:

- Sickle cell disease and other hemoglobinopathies*

METABOLIC CONDITIONS:

AMINO ACID CONDITIONS:

- Homocystinuria*
- Hyperphenylalanemia, including phenylketonuria (PKU)
- Tyrosinemia*

FATTY ACID OXIDATION CONDITIONS:

- Carnitine uptake defect
- Carnitine palmitoyl transferase I deficiency (CPT I)*
- Carnitine palmitoyl transferase II deficiency (CPT II)
- Multiple acyl-CoA dehydrogenase deficiency (MADD)
- Short chain acyl-CoA dehydrogenase deficiency (SCAD)
- Medium chain acyl-CoA dehydrogenase deficiency (MCAD)±
- Long chain 3 hydroxyacyl-CoA dehydrogenase deficiency (LCHAD)*±
- Very long chain acyl-CoA dehydrogenase deficiency (VLCAD)*±

ORGANIC ACID CONDITIONS:

- Beta-ketothiolase deficiency (BKD)±
- Glutaric acidemia, Type I (GA I)*
- Isobutyryl CoA dehydrogenase deficiency (IBD)±
- Isovaleric acidemia (IVA)* ±
- Malonic aciduria
- Maple syrup urine disease (MSUD)±
- Methylmalonic acidemias (MMA/8 types)±

- Propionic acidemia (PA)*±
- 3-Hydroxy-3-methylglutaryl CoA lyase deficiency (HMG)*
- 2-Methyl-3-hydroxybutyryl CoA dehydrogenase deficiency (MBHD)*
- 2-Methylbutyryl CoA dehydrogenase deficiency (2MBC)*
- 3-Methylcrotonyl CoA carboxylase deficiency (3MCC)
- 3-Methylglutaconyl CoA hydratase deficiency (3MGH)
- Multiple carboxylase deficiency

UREA CYCLE CONDITIONS:

- Arginase deficiency
- Argininosuccinate lyase deficiency (ASA)±
- Citrullinemia±

OTHER CONDITIONS:

- Biotinidase deficiency
- Galactosemia±

* The screening test will not detect 100 percent of affected infants.

± Represent emergent conditions. Infants are at risk of illness or death in the first week or two of life.

The purpose of newborn screening is to identify infants at risk that require more definitive testing. As with any laboratory test, both false negative and false positive results are possible. Screening test results are insufficient information on which to base diagnosis or treatment.

Table I summarizes the conditions on the New Mexico screening panel, including the incidence, symptoms, and treatment.

Disorders	Analyte tested for	Incidence in NW region	Symptoms if not treated	Treatment
Cystic fibrosis	Immunotrypsinogen (IRT)	1:3,500	Lung disease; growth failure	Pulmonary therapy, prevent infection, replace digestive enzymes
Congenital adrenal hyperplasia (CAH)*	17-OH-Progesterone	1:12,000 1:300 in Yupik Eskimos	Addisonian crisis/salt wasting in 3/4 infants; dehydration; shock; hyperkalemia; virilization of females	Glucocorticoid and/or mineralocorticoid (Florinef)
Congenital hypothyroidism	Thyroid hormones (T4 and TSH)	1:3,000	Mental retardation; other brain damage; growth delay	Thyroid hormone (L-Thyroxine)
Hemoglobinopathies including sickle cell disease	Hemoglobin patterns	1:5,000 (1:400 in African Americans)	In sickle cell disease: death by sepsis or splenic sequestration anemia; sickling crisis	Penicillin and comprehensive care
Biotinidase deficiency	Biotinidase	1:60,000	Mental retardation; seizures; skin rash; alopecia; hearing loss; death	Biotin
Galactosemia	Galactosemia enzyme (GALT)	1:60,000	Severe brain damage; liver disease; cataracts; death	Galactose-restricted diet
Argininase deficiency	Arginine	1:300,000	Irritability; developmental delay; spastic tetraplegia	Low protein diet, medication
Arginosuccinate lyase deficiency (ASA)*	ASA/Citrulline	1:70,000	Hyperammonemia; mental retardation; seizure; death	Low protein diet, medication
Arginosuccinate synthetase deficiency (Citrullinemia)*	Citrulline	1:57,000	Hyperammonemia; mental retardation; seizure; death	Low protein diet, medication
Homocystinuria	Methionine	1:100,000	Mental retardation; dislocation of lenses; marfanoid body habitus	Pyridoxine; methionine restricted, cysteine supplemented diet
Hyperphenylalaninemia, including phenylketonuria (PKU)	Phenylalanine	1:13,000	Profound mental retardation; seizures	Low phenylalanine diet
Tyrosinemias (Transient, Type I & Type II)	Succinylacetone/ Tyrosine	1:100,000	Vomiting; lethargy; liver disease; coagulopathy; renal tubular acidosis	Medication; low phenylalanine and/or low tyrosine diet
Beta-ketothiolase deficiency (BKD)	C5:1, C5OH	rare, > 1:300,000	Severe bouts of acidosis possibly resulting in mental retardation, death	IV support during episodes, bicarbonate supplement

* Infants may have severe neonatal presentation.

(continued on next page)

Table I (continued)

Disorders	Analyte tested for	Incidence in NW region	Symptoms if not treated	Treatment
Glutaric acidemia, Type I (GA I)	C5DC	1:71,000	Often asymptomatic in newborn; sudden metabolic crisis damages basal ganglia	IV support during intercurrent illness, protein restriction, carnitine therapy
Isobutyryl CoA dehydrogenase deficiency (IBD)	C4	rare, > 1:300,000	None to cardiomyopathy	Carnitine therapy, protein restriction, avoid fasting
Isovaleric acidemia (IVA)	C5	1:90,000	Vomiting; lethargy; acidosis possibly resulting in coma, death	Protein restriction, carnitine and glycine therapy
Malonic aciduria	C3DC	rare, > 1:300,000	Mental retardation	Carnitine therapy, protein restriction
Maple syrup urine disease (MSUD)*	Leucine	1:200,000	Vomiting; lethargy; acidosis possibly resulting in death	Protein restriction, avoid fasting
Methylmalonic acidemias (MMA/8 types)*	C3, C3/C2	1:50,000	Vomiting; lethargy; acidosis possibly resulting in death	Protein restriction, carnitine therapy, hydroxocobalamin therapy
Multiple Carboxylase Deficiency (MCD)	C3, C5OH	> 1:60,000	Hypotonia, seizures, skin rash, alopecia, lactic acidosis, brain damage. Average age at presentation: birth–18 months	Biotin
Propionic acidemia (PA)*	C3, C3/C2	> 1:100,000	Vomiting; lethargy; acidosis possibly resulting in death	Protein restriction, carnitine therapy
3-hydroxy-3-methylglutaryl CoA lyase deficiency (HMG)	C5OH	rare, > 1:300,000	Hypoglycemia; acidosis possibly resulting in death; may be asymptomatic	Protein restriction
2-methyl-3-hydroxybutyryl CoA dehydrogenase deficiency (MHBD)	C5:1, C5OH	rare, > 1:350,000	Asymptomatic 9–14 mos. Then severe mental and motor skill loss. Hmong infants may be asymptomatic	Protein restriction
2-methylbutyryl CoA dehydrogenase deficiency (2MBC)	C5	rare, > 1:300,000 Increased incidence among Hmong	Hypoglycemia; mental retardation; Hmong infants may be asymptomatic	None or avoid fasting.
3-methylcrotonyl CoA carboxylase deficiency (3MCC)	C5OH	1:50,000	Most have been asymptomatic	None or protein restriction; carnitine therapy if deficient

* Infants may have severe neonatal presentation.

(continued on next page)

Table I (continued)

Disorders	Analyte tested for	Incidence in NW region	Symptoms if not treated	Treatment
3-methylglutaconyl CoA hydratase deficiency (3MGH)	C5OH	rare, >1:300,000	Hypoglycemia; acidosis; may be asymptomatic	Protein restriction, avoid fasting
Short chain acyl-CoA dehydrogenase deficiency (SCAD)	C4	1:43,000	Most asymptomatic; hypotonia, mental retardation	Avoid fasting during periods of catabolism
Medium chain acyl-CoA dehydrogenase (MCAD)*	C6, C8, C10, C8/C10	1:15,000	Hypoglycemia possibly resulting in coma, death; may be asymptomatic	Avoid fasting, carnitine supplement
Long chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHAD)	C14:1, C16, C16OH, C18, C18OH,	1:50,000	Hepatic dysfunction; hypoglycemia; failure to thrive	Long chain fatty acid restriction, Medium Chain Triglycerides (MCT) oil, carnitine, avoid fasting
Very long chain acyl-CoA dehydrogenase deficiency (VLCAD)	C14, C14:1, C16, C16:1, C18, C18:1,	1:31,000	Hypoglycemia with or without cardiomyopathy; muscle fatigue	Avoid fasting, low fat diet with MCT oil
Carnitine uptake/transport defects	C0, C16, C18	1:50,000	Hypoglycemia; cardiomyopathy	Avoid fasting, low fat diet, carnitine supplement
Carnitine palmitoyl transferase I deficiency (CPT I)	C0/C16+C18	rare, >1:300,000 Increased in Hutterite and Alaska native populations	Hypoketotic hypoglycemia, brought on by fasting or intercurrent illness. Average age at presentation: birth–18 months	Avoid fasting and long chain fatty acids; MCT oil supplement
Carnitine palmitoyl transferase II deficiency (CPT II)	C0, C4, C5, C6, C14, C16, C16:1, C18, C18:1	rare, >1:300,00	Muscle weakness, pain and myoglobinuria leading to renal failure in 25%. Average age at presentation: 15–30 yrs; also a severe neonatal form usually lethal with multiple congenital anomalies	Avoid fasting and severe exercise; MCT oil supplement
Multiple acyl-CoA dehydrogenase deficiency (MADD) also known as Glutaric acidemia type II	C4, C5, C6, C8, C10, C14, C16, C18:1	rare, >1:300,000	Multiple congenital abnormalities; acidosis, hypoglycemia	Low fat diet, avoid fasting, not effective in severe neonatal form

* Infants may have severe neonatal presentation.

Table II summarizes normal laboratory values and laboratory criteria used for follow-up. Phone follow-up (with mail confirmation) is provided for significantly abnormal test results. Mail follow-up is provided for normal and mildly abnormal results. More information on these conditions is available on Oregon Department of Human Services website: www.oregon.gov/DHS/ph/nbs/expand.shtml. See additional information on MS/MS conditions in **Appendix I**.

Analyte	Normal***	Follow-up by medical consultant/NBS nurse**	Follow-up by mail
Thyroxine	Upper 90% of T4 determinations	T4 in lower 10% and TSH > 100 μ UI/mL-	T4 < 5.0 μ mg/dL, TSH normal (low birth weight infant)
TSH	≤ 60 μ UI/mL if 0–11 hrs old ≤ 35 μ UI/mL if 12–48 hrs old ≤ 25 μ UI/mL if > 48 hrs old	> 200 μ UI/mL if 0–11 hrs old > 100 μ UI/mL if 12–23 hrs old > 60 μ UI/mL if 24–48 hrs old > 35 μ UI/mL if > 48 hrs old	60.1–200 μ UI/mL if 0–11 hrs old 35.1–100 μ UI/mL if 12–23 hrs old 35.1–60 μ UI/mL if 24–48 hrs old 25.1–35 μ UI/mL if > 48 hrs old
17-OH-Progesterone*	≤ 90 ng/mL 0-10 days old, ≤ 40 ng/mL > 10 days old, BW < 2500 g ≤ 70 ng/mL < 24 hrs old, ≤ 40 ng/mL 1-10 days old, ≤ 25 ng/mL > 10 days old, BW ≥ 2500 g	> 150 ng/mL if < 24 hrs old, > 120 ng/mL if 1-10 days old, > 70 ng/mL > if 10 days & BW < 2500 g > 100 ng/mL if < 24 hrs old, > 60 ng/mL if 1-10 days old, > 50 mg/mL if > 10 days & BW ≥ 2500 g	> 90-150 ng/mL if < 24 hrs old, > 90-120 ng/mL if 1-10 days old, > 40-70 ng/mL > if 10 days & BW < 2500 g, > 70-100 ng/mL if < 24 hrs old, > 40-60 ng/mL if 1-10 days old, > 25-50 mg/mL if > 10 days & BW ≥ 2500 g
Hemoglobin IEF/HPLC	Hgb F and A	Probable homozygote	Probable heterozygote
Biotinidase	Activity present	Activity absent	Partial activity
Galactosemia enzymes (Galactose, Gal-1-P04 and GALT)	Enzyme activity present	No enzyme activity present AND galactose ≥ 20 mg/dL OR galactose < 20 mg/dL if age < 48 hrs	No enzyme activity present AND galactose < 20 mg/dL AND age ≥ 48 hrs OR Reduced enzyme activity AND galactose ≤ 30 mg/dL
Arginine	≤ 110 μ M/L	> 180 μ M/L	> 110 & ≤ 180 μ M/L
ASA*	≤ 1.5 μ M/L	> 1.5 μ M/L	
Citrulline*	≤ 70 μ M/L 1st NBS ≤ 120 μ M/L 2nd NBS	> 70 μ M/L 1st NBS	> 120 μ M/L & ASA ≤ 1.5 μ M/L 2nd NBS
Leucine*	≤ 270 μ M/L & Leu/Ala ≤ 1.6 1st NBS ≤ 350 μ M/L & Leu/Ala ≤ 1.6 2nd NBS	> 270 μ M/L & Leu/Ala > 1.6 1st NBS > 350 μ M/L & Leu/Ala > 1.6 2nd NBS	
Methionine	≤ 80 μ M/L 1st NBS ≤ 100 μ M/L 2nd NBS	> 190 μ M/L on 1st or 2nd NBS	> 80 μ M/L & < 190 1st NBS > 100 μ M/L & < 190 2nd NBS
Phenylalanine	≤ 190 μ M/L	> 190 μ M/L and Phe/Tyr > 3.0	> 190 μ M/L & Phe/Tyr < 3.0
Tyrosine	≤ 480 μ M/L	> 480 μ M/L on requested NBS in 2-3 months	> 480-680 μ M/L - NBS within 3 weeks > 680 μ M/L - NBS requested in 2-3 months

* Infants may have severe neonatal presentation.

**All phoned results are followed by mailed confirmation. All of these tests are screening tests. Abnormal results need full evaluation/discussion with a consultant before a diagnosis is confirmed or treatment is started.

***Normal and abnormal values are subject to change based on continuing statistical evaluation.

(continued on next page)

Table II (continued)

Analyte	Normal***	Follow-up by medical consultant/NBS nurse**	Follow-up by mail
Succinylacetone	≤ 1.5 μM/L	> 1.5 μM/L	
C0	≥ 7.5 μM/L & < 300 μM/L	< 7.5 μM/L 1st & 2nd NBS, BW > 2500 g or not on parenteral nutrition	< 7.5 μM/L 1st NBS, BW > 2500 g or not on hyperal < 7.5 μM/L 1st & 2nd NBS, BW < 2500 g or on hyperal
C0/C16+18	≤ 100	> 100	
C3*	≤ 7.5 μM/L & C3/C2 ≤ 0.40	> 7.5 μM/L & C3/C2 > 0.40	> 7.5 μM/L & C3/C2 ≤ 0.40
C3DC	≤ 0.50 μM/L	> 0.50 μM/L	
C4	≤ 1.4 μM/L	> 2.1 μM/L	> 1.4 μM/L & ≤ 2.1 μM/L
C5	≤ 0.70 μM/L 1st NBS ≤ 1.10 μM/L 2nd NBS	> 0.70 μM/L 1st NBS	> 1.10 μM/L 2nd NBS if on hyperal & 1st NBS normal
C5:1	≤ 0.15 μM/L	> 0.15 μM/L	
C5OH	≤ 1.50 μM/L	> 1.50 μM/L	> 1.50 μM/L & ≤ 2.30 μM/L
C5DC	≤ 0.70 μM/L, C5DC/C8 ≤ 11.5, C5DC/C16 ≤ 1.5	> 0.70 μM/L, C5DC/C8 > 11.5, C5DC/C16 > 1.5	
C6, C8, C10*	≤ 0.80 μM/L, ≤ 0.70 μM/L, ≤ 0.70 μM/L	> 0.80 μM/L, > 0.70 μM/L, > 0.70 μM/L	
C14	≤ 0.80 μM/L	> 0.80 μM/L if other long chain analytes elevated	> 0.80 μM/L only elevation
C14:1	≤ 0.70 μM/L	> 1.00 μM/L if other long chain analytes elevated	> 0.60 μM/L & ≤ 1.0 μM/L
C16	≤ 8.0 μM/L	> 8.0 μM/L if other long chain analytes elevated	> 8.0 μM/L only elevation
C16:1	≤ 0.80 μM/L	> 0.80 μM/L if other long chain analytes elevated	> 0.80 μM/L only elevation
C16OH	≤ 0.10 μM/L	> 0.10 μM/L if other long chain analytes are elevated	> 0.10 μM/L only elevation
C18	≤ 3.10 μM/L	> 3.10 μM/L if other long chain analytes are elevated	> 3.10 μM/L only elevation
C18:1	≤ 4.50 μM/L	> 4.50 μM/L if other long chain analytes are elevated	> 4.50 μM/L only elevation
C18:1OH	≤ 0.20 μM/L	> 0.20 μM/L if other long chain analytes are elevated	> 0.20 μM/L only elevation
C18OH	≤ 0.10 μM/L	> 0.10 μM/L if other long chain analytes are elevated	> 0.10 μM/L only elevation
Immunotrypsinogen (IRT)	≤ 90 ng/mL 1st NBS ≤ 60 ng/mL 2nd NBS	> 90 ng/mL 1st NBS > 60 ng/mL 2nd NBS	> 90 ng/mL 1st NBS

* Infants may have severe neonatal presentation.

**All phoned results are followed by mailed confirmation. All of these tests are screening tests. Abnormal results need full evaluation/discussion with a consultant before a diagnosis is confirmed or treatment is started.

***Normal and abnormal values are subject to change based on continuing statistical evaluation.

Definition

Screening practices are the actions and decisions of practitioners regarding the collection, handling and follow-up of newborn screening specimens. Practitioners are integral to the newborn screening in that they are responsible for collection and handling of specimens for every infant in their care, parent education and prompt action on incomplete or abnormal results referred to them. In the event an infant is affected, the practitioner's actions and decisions to ensure rapid evaluation and appropriate treatment can have lifelong implications for the infant and the family.

Who is responsible for ensuring that the screening test is performed?

New Mexico's statutes require that all hospitals or institutions having facilities, for childbirth perform or have performed screening tests for congenital diseases on all New Mexico newborn infants prior to discharge. New Mexico is a two screen state, requiring the first screen be done prior to discharge. If the infant is not born in a hospital, the attending physician, nurse, nurse-midwife, midwife or responsible person is responsible for assuring that a newborn screen is collected.

Parent refusal to have the infant screened

A parent may refuse screening for personal and/or religious beliefs. Parents may be influenced by the attitude of their practitioner toward newborn screening, and the majority agree to screening if properly counseled about the importance of early detection. Infants have been harmed as a result of practitioners who have advised against screening as the "conditions were too rare," or "we don't

want to poke the infant," or "the second test is not really necessary."

In the event that parents are adamantly opposed to screening, it is the responsibility of the practitioner to fully inform them about the process and all screening conditions and to obtain a signed Newborn Screening Test Refusal (informed dissent) document. This document is placed in the infant's medical record with a copy given to the parents, and copies forwarded to both the New Mexico Newborn Screening Program

Table III - Validity of 1st and 2nd NBS tests

Disorder	Percent detected - first test	Percent detected - second test
Cystic Fibrosis	>95	NA
Hemoglobinopathies	>99	NA
Hypothyroidism	90	10
Congenital Adrenal Hyperplasia	95	5
Phenylketonuria	>99	1
MSUD	>99	1
Other Amino Acidopathies	50-90	10-50
Galactosemia	>99	1
Biotinidase Deficiency	99	0
Fatty Acid Oxidation Disorders	90	10
MCAD	95	5
CPT1 (Alaska Native)	55	45
Carnitine uptake	40	60
LCHAD/VLCAD	85	15

and the primary care provider. Failure to do so may result in significant practitioner and facility liability if an affected infant is not screened and subsequently harmed. Unfortunately, informed dissent does not confer protection from liability, but can limit damage in some cases. A sample statement of parental refusal is given on [page 33](#) or the hospital's form may be used.

Screening before discharge

All birthing facilities, including birth centers in New Mexico, are required to practice uniform discharge screening regardless of the age or feeding status. This process is done because some infants do not return for routine post-natal care and most of the tests are valid at any age. Failure to collect a specimen before discharge may result in a significant liability on both the facility and responsible practitioner if an affected infant is missed.

Proper time for specimen collection

There are over 20 conditions on the screening panel that can kill or maim in the first week or two of life; however, another three to four may not show any abnormal results until the second or third week of life. Improved technology in the laboratory makes the issue of milk ingestion less important than it was in the past.

Specimens obtained prior to 48 hours of age are valid for most of the conditions covered on the newborn screening panel. There is, however, a statistical chance that certain amino acid and endocrine disorders, urea cycle defects and FAO disorders may be missed. In the NWRNSP, 10–12 percent of those with hypothyroidism, CAH and certain disorders detected via MS/MS are found only on the second specimen as outlined in [Table III](#).

NORMAL NEWBORNS:

In New Mexico, all infants must have two specimens. For normal, non-premature infants, the first specimen should be collected before discharge, ideally between 24–48 hours, but due to the number and severity of emergency metabolic conditions and CAH it is felt an earlier specimen is preferable. A second specimen must be collected between 10–14 days of age on all infants. Infants born at home should also be screened at these times. A parental refusal form should be signed if screening is refused.

PREMATURE, LOW BIRTH WEIGHT OR SICK INFANTS: All Neonatal Intensive Care Units (NICU) in our region are strongly urged to practice “admission screening” before any non-respiratory therapy is started. In some cases the infants may only be minutes or a few hours old. This is followed by a second specimen between 48–72 hours of age and a third specimen at 28 days or at discharge, whichever comes first. A special three-part kit is available for NICU infants. (See [page 30](#).)

DYING INFANTS:

If an infant is likely to die, especially if there is no apparent cause for death, it is appropriate to collect a newborn screening specimen. In addition, collect a urine specimen, which should be frozen immediately. While dying infants may have abnormal amino acids as a normal response to organ failure, the blood may also provide a diagnosis of an early onset screening disorder or be a source of DNA for future diagnostic studies. In many cases, the blood spots have been the only source of DNA available for that infant and have been a valuable resource for families.

OLDER INFANTS

The American Academy of Pediatrics recommends that physicians know the screening status of every child in their care. Older infants and children may enter the practice without evidence of screening, or the physician may be suspicious of a screenable condition. Unfortunately, OSPHL has established standards and cutoffs for newborns and infants only up to 6 months of age. These values are not applicable nor reliable for older infants and children. OSPHL therefore, cannot accept specimens for children older than 6 months of age.

Table IV - Age of infant at specimen collection*

Infant type	1st specimen	2nd specimen	3rd specimen
NORMAL INFANT (hospital, birth center and home births)	Ideal: 24-48 hours of age* Acceptable: 0-23 hours	Ideal: 10-14 days Acceptable: 3-5 days if first specimens collected 0-23 hours of age.	n/a
PRETERM, LOW BIRTH WEIGHT OR SICK INFANTS	Upon admission (any age)* Before red cell transfusion Before any non-respiratory therapy is started	48–72 hours of age; if still in NICU	3rd specimen at 28 days or if discharge prior see Appendix II .
OLDER INFANTS (>6 months)	Diagnostic tests only Blood spots may be used**	Not needed	Not needed
DYING INFANTS (of unknown cause)	Four full blood spots (any age) Urine frozen ASAP	n/a	n/a

*These recommendations are different than those recommended in New Mexico Administrative Rules. New Mexico Administrative Rules are in the process of revision to meet the new screening lab recommendations. Practitioners should follow the recommendations above.

**Please see [page 15](#) for a listing of the metabolic laboratory that can provide Tandem Mass Spectrometry (MS/MS) testing on older children. Also listed, are recommendations for further diagnostic testing for the other disorders on the newborn screening battery. These laboratories are listed for your convenience only. You may send your specimen to any accredited laboratory that provides the appropriate testing.

We highly recommend proceeding directly to diagnostic testing if there are signs or symptoms of a metabolic disorder present in the child (see below).*

Diagnostic laboratories for screening older children and/or adults

Also listed are recommendations for further diagnostic testing for the other disorders in the newborn screening battery. *These laboratories are listed for your convenience only. You may send your specimen to any accredited laboratory that provides the appropriate testing.*

- **MS/MS TESTING (AKA EXPANDED OR SUPPLEMENTAL NEWBORN SCREENING):**

Includes testing for selected amino acid, fatty acid, organic acid and urea cycle disorders.

Baylor University Medical Center at Dallas
3812 Elm Street
Dallas, Texas 75226
Telephone: 214-820-4533
www.baylorhealth.edu/imd

- **BIOTINIDASE DEFICIENCY:**

Biotinidase enzyme assay
Biochemical Genetics Laboratory
University of Maryland, School of Medicine
Division of Human Genetics
BRB 11-047, 665 West Baltimore Street
Baltimore, Maryland 21201
Telephone: 410-706-2810

- **CONGENITAL HYPOTHYROIDISM:**

Serum – Free T₄, TSH can be done at most local laboratories.

SICKLE CELL DISEASE:

Isoelectric Focusing/High Performance Liquid Chromatography can be done at most local laboratories.

Never use Sickledex.

- **GALACTOSEMIA:**

Galactose-1-Phosphate
Galactose-1-Phosphate Uridyl Transferase
University Children's Genetic Laboratory
116 East Broadway
Glendale, CA 91205
Telephone: 818-548-0999
Fax: 818-548-1555

- **CONGENITAL ADRENAL HYPERPLASIA:**

Serum 17-OH-Progesterone can be done at most local laboratories.

Specimen collection before transfer of infant to another facility

- New Mexico Newborn Screening Program specifies that infants who are transferred to another facility within 48 hours of birth should be tested by the receiving facility. (See timing of specimen collection on page 12.) If an NBS kit has been issued by the birth hospital to the infant, it can be sent with the infant ensuring that both facilities are notified of the results.

Patient demographic information

Accurate patient information is critical for rapid follow-up in the event of abnormal results. Be sure to use the correct part of the kit: PART 1 for the first specimen and PART 2 for the second specimen, and for NICU infants, PART 3 for the third specimen. Failure to do so makes it difficult to track the infant's results. In addition, hemoglobin and cystic fibrosis testing is done only on the first specimen.

The laboratory form should be completed with the information requested. This information is required by Clinical Laboratory Improvement Amendments of 1988 (CLIA) and is part of the legal record and must be legible. Infant's name, birth date and time, specimen collection date and time and physician's name are particularly important. Please name the physician who will be responsible for this infant's care after discharge, not the resident or on-call physician who may have seen the infant in the hospital. In the event of an abnormal test result, the physician and/or facility named on the card is legally obligated to locate the infant. Do not use plastic imprint cards, as they often produce unreadable information and cause compression damage to the filter paper. All demographic data should be completed before the blood is drawn to avoid contamination of the specimen. The person collecting the specimen is required to sign the form. In New Mexico, a second contact name and number is required to assist in follow-up.

Specimen transport

If lives are to be saved, it is critically important that the OSPHL receives newborn screening specimens as soon as possible after collection. Ideally, specimens should be mailed or transported as soon as they are dried (2–4 hours) and no later than 24 hours after collection. Many of the conditions on the screening battery kill or maim infants in the first week of life. To prevent this, diagnosis and treatment must occur rapidly. In New Mexico, the newborn screening program uses courier services for first specimens and second specimens may be sent through regular mail unless otherwise instructed. Significant degradation of hemoglobin and some analytes also occurs in specimens older than one week.

New Mexico's Newborn Screening Program has contracted with UPS to be the overnight courier for New Mexico's shipment of first screens. Hospitals or midwives should report any issues with the UPS shipment of specimen to the Newborn Screening Program 505-476-8868.

If a courier is used, it is advisable to establish a list of specimens sent and to document the time of

specimen pickup and delivery. This simple practice protects the submitter if specimens are lost in transit.

Newborn screening for preterm, low birth weight or sick infants

Newborn screening for premature, low birth weight (LBW) or sick infants can be complex and sometimes frustrating as they generate more false positive results than normal infants, are more likely to have

the screening test forgotten, and are at a greater risk of having false negative results. Maternal conditions and treatments, the infant's immaturity and/or illness and the critical nature of their care conspire to interfere both with the collection of the specimens and interpretation of results. Some of the problems unique to these infants are outlined in Tables V–VII.⁶

Table V: Maternal conditions affecting the newborn screening results

Maternal conditions	NBS analyte affected	Results in	Additional information/ duration of interference
Hyperthyroidism treated with Propylthiouracil (PTU)	Low thyroxine (T4), high TSH	Transient hypothyroidism	Until drug clears, typically 7–14 days
¹³¹ I (radioactive iodine) treatment during pregnancy: Before 8 weeks' gestation.	none	Euthyroid (but may cause birth defects)	Will cause maternal hypothyroidism (potential effect on fetal brain development if not treated in first trimester)
¹³¹ I (radioactive iodine) treatment during pregnancy: After 8 weeks' gestation (when fetal thyroid matures and traps iodine)	Low T4, high TSH	Permanent hypothyroidism	Lifelong
Steroids: prednisone, betamethasone/dexamethasone	Low or normal 17-OHP	Suppresses fetal adrenal function and causes false-negative results for CAH	Unknown - depends on class of steroid and dose; estimate 1–2 weeks
CAH	Elevated 17-OHP	False-positive result	Unknown-estimate 3-7 days
PKU or moderate hyperphenylalaninemia uncontrolled by diet or medications	Elevated phenylalanine; although ratio of phenylalanine - to - tyrosine (Phe/Tyr) should be normal; false-positive result	Transient hyperphenylalaninemia	12–24 hours unless infant has PKU
3-MCC deficiency	Elevated C50H	False-positive result	Unknown
Fatty liver of pregnancy or HELLP syndrome (hemolysis, elevated liver enzymes, low platelets)	May have elevated even chain acylcarnitines	False-positive result	Unknown
Carnitine deficiency	May have low carnitine levels	False-positive result	Unknown
Vitamin B12 deficiency	Elevated propionylcarnitine (C3)	False-positive result	A number of days depending on nutrition provided

CLSI. Newborn Screening for Preterm, Low Birth Weight, and Sick Newborns; Approved Guideline. CLSI document I/LA31-A. Wayne, PA: Clinical and Laboratory Standards Institute; 2009.

Table VI: Treatments used in special care baby unit and effects on newborn screening results

Treatment	Effect on newborn screening results	Duration of effect
Parenteral Nutrition (PN)	Elevation of multiple amino acids	4–24 hours after PN discontinued
Carnitine supplementation	Elevations of acylcarnitines; can mask carnitine transport disorders	For duration of supplementation and weeks later
Red cell transfusion and Extra Corporeal Life Support (ECLS) (pre- and postnatal transfusions)	Can mask the absence of enzymes and proteins intrinsic to the red blood cell (RBC), thereby negating results for hemoglobinopathies and galactosemia (when testing is for galactose 1 phosphate uridylyl transferase (GALT) enzyme activity)	120 days after last transfusion ECLS invalidates all NBS results for analyte-specific periods of time
Dopamine	False-negative testing for CH, because levels of TSH are suppressed	Until drug therapy is stopped
Steroids	Suppressed TSH and T4; possible false-negative result for CH. May suppress 17-OHP resulting in false-negative testing for CAH	Unknown - depends on class of steroid and dose; estimate 1–2 weeks
Iodine exposure with povidone/iodine preps	Transient hypothyroidism; low T4, elevated TSH	Once exposure to topical iodine discontinued, resolution may take 2–6 weeks (depending on dose absorbed and other factors)
Pivalic acid antibiotic therapy	May cause elevated isovaleryl 2-methylbutyryl carnitine	Unknown

Table VII: Conditions of the infant affecting newborn screening tests

Condition of the infant	Effect on newborn screening	Duration of effect
Immature hypothalamic-pituitary thyroid axis	Low T4, normal TSH, infants with congenital hypothyroidism (CH) can be missed	Up to 6 weeks of age
Hypothyroxinemia of preterm birth	Transient hypothyroidism, low T4; normal TSH followed by elevated TSH	Up to 6 weeks of age
Liver enzyme immaturity	Transient elevations of tyrosine, methionine, and galactose, occasionally other amino acids	A few weeks
Iodine deficiency	Transient hypothyroidism low T4, elevated TSH	Until supplemented
Acute illness	Transient hypothyroidism; low T4, elevated TSH, elevated immunoreactive trypsinogen (IRT)	Until recovered
Hypoxia	Elevated IRT	Until recovered
Liver disease	Elevated tyrosine, methionine, galactose Depression of biotinidase enzyme	Until recovered
Renal immaturity	Elevated 17-OHP, amino acids	Until recovered
Preterm	Lower biotinidase levels inversely related to gestational age	40 weeks gestational age

Maternal conditions and treatments affecting NBS results

MATERNAL CONDITIONS

- **Thyroid dysfunction:** Hypothyroid mothers on adequate replacement therapy during pregnancy deliver infants with normal thyroid function. Maternal hyperthyroidism treated with propylthiouracil (PTU) during pregnancy may result in transient hypothyroidism in the infant. Inadvertent treatment with radioactive iodine after 8 weeks gestation may result in permanent hypothyroidism in the infant. Mothers who ingest megadoses of iodine during pregnancy may have infants with hypothyroidism.
- **Steroids:** These are frequently given to mothers during pregnancy and may suppress fetal adrenal function resulting in false negative 17-OH progesterone in the infant affected with congenital adrenal hyperplasia.
- **Fatty liver of pregnancy or HELLP syndrome (hemolysis, elevated liver enzymes, low platelets):** Increased risk of fetus with fatty acid oxidation disorder or a normal fetus with transiently elevated acylcarnitines.
- **Maternal CAH, PKU and 3-MCC deficiencies** may result in transient elevations of respective analytes in infant.
- **Maternal carnitine deficiency:** may result in low carnitine levels in the infant.
- **Maternal B12 deficiency:** may result in elevated propionylcarnitine (C₃).

TRANSIENT HYPOTHYROXINEMIA OF PREMATURITY (THOP):

The hypothalamic-pituitary-thyroid (HPT) axis is not functioning properly in premature infants and it is positively correlated with gestational age. In addition, sick and premature infants have a greater need for thyroxine and topical iodine skin cleansers depress T₄. As a result T₄ levels can be quite low for a week or more; TSH levels are usually normal. The significance of THOP on later development is still unknown due to the lack of well controlled long term outcome studies, but is thought to be somewhat benign. While a low T₄ and an elevated TSH are the classic hallmarks of congenital hypothyroidism, some infants with CH have a delayed rise in their TSH, so practitioners cannot assume a premature or sick infant with a low T₄ only has THOP and not CH. Serial screening specimens for T₄/TSH are required until the T₄ normalizes.

ANTIBIOTIC THERAPY:

Antibiotics containing pivalic acid (for example: piperacillin, pivmecillinan, cefditorempivoxil) given to mothers during labor or to newborns may cause false elevation of isovaleryl/2-methyl butyryl carnitine. Be sure to specify this antibiotic on the request slip if it has been used.

PARENTERAL NUTRITION AND CARNITINE THERAPY:

These are not contraindications to screening, but samples should not be taken from the line that is used to deliver the nutrition or drugs. High levels of several amino acids can occur during parenteral nutrition and are the most common reason for "mixed elevations." Carnitine, added to intravenous solutions or formulas,

may mask the biochemical markers for carnitine acylcarnitine translocase deficiency or carnitine palmitoyl transferase deficiency, type II. Screening specimens must be repeated after these therapies are discontinued. Be sure to specify these therapies on the request slip.

RED CELL TRANSFUSIONS:

A specimen should be obtained before the transfusion as donor cells provide normal levels of enzymes and hemoglobins and may temporarily normalize certain metabolites. Metabolite tests (e.g., phenylalanine, carnitine, galactosemia) will become abnormal after a few days regardless of the transfusion. It may take as long as 120 days for infants to develop abnormal enzyme levels and hemoglobins after a transfusion, significantly delaying diagnosis and treatment. This is the rationale for admission screening for every NICU infant. An early screening test, before these interventions are begun, has been life saving for affected infants in the past. While only a small percentage of infants receive red cell transfusions, it has been impossible to establish policies and procedures in NICUs that ensure specimen collection before transfusion. Furthermore, even with aggressive follow up and the assistance of local physicians we are able to obtain a valid screening test on less than 40 percent of the transfused infants three months after the last transfusion. For affected infants, damage will have accrued during this time, increasing the liability to the physician, hospital, state and program.

Transient abnormalities

While NICU admission screening is strongly recommended, some premature/sick infants tested in the first few hours of life may have an increased chance of false positive results from elevated thyroid stimulating hormone (TSH) and/or 17-OH-progesterone. These levels are generally elevated in the first 24 hours after birth as a reaction to stress, falling into normal range a day or two later. A recent study of infants in the NWRNSP who were tested on admission showed that an additional 4 percent of NICU infants had elevated TSH on these early specimens, but 99 percent resolved on the second test. Also, a very early specimen is not valid for many of the amino acids, such as phenylalanine or leucine, but these metabolites rise independent of transfusions and should be identified on the second test. We believe NICU admission screening improves screening for infants who will receive transfusions without creating an undue number of false positives.

Clinical signs or family history

A number of clinical situations will modify the usual approach of obtaining a newborn screening specimen and waiting for the result. The following are suggested guidelines for particular situations that may arise.

When in doubt about the course of management for any of the conditions on the screening test, consultation with a specialist is advised. The directory on page 1 offers consultants by disease to assist with screening and confirmation testing.

INFANTS WHO EXHIBIT CLINICAL SIGNS AND SYMPTOMS:

The newborn screening test, like any laboratory test, may have false positives and false negatives.

If signs and symptoms of one of the newborn screening conditions are clinically evident, the physician should proceed to diagnostic testing, pending the results of the screen or in spite of the results of the screen. It may be necessary to treat as if the infant has the condition. Medical consultation is available 24-hours, 7 days a week for assistance for rapid diagnosis and institution of treatment for infants suspected to have disease. Common laboratory tests available locally may help distinguish conditions. These include:

- CAH: electrolytes
- FAO disorders: glucose
- OA disorders: arterial blood gas, add complete metabolic panel
- Urea cycle disorders: ammonia, glucose.

IF THE RESULTS OF THE NEWBORN SCREEN ARE PENDING:

For any of the screened conditions, but especially those in which the metabolite accumulation can be life threatening such as adrenal hyperplasia or many of the metabolic conditions, contact a consultant specialist for instructions on further evaluation of the patient.

IF THE NEWBORN SCREENING TEST RESULT WAS “NORMAL”:

If clinical symptoms suggest one of the screened conditions despite a “normal” screening result, the physician should proceed as if the patient has the condition and immediately contact a consultant specialist for instructions on further evaluation of the patient. If the infant was found to be affected, notify the OSPHL and the New Mexico Newborn Screening Program as soon as possible.

NEWBORN SCREENING OF AN INFANT WITH AN AFFECTED SIBLING OR OTHER CLOSE RELATIVE:

As many of the conditions tested for by newborn screening are genetic, it is possible that multiple members of a family may be affected. Prenatal diagnosis is possible for many of these conditions; if prenatal diagnosis determines that the infant is affected, any appropriate treatment (e.g., special diet) should be initiated immediately after birth. If prenatal diagnosis predicts an unaffected infant, practitioners should bear in mind that no prenatal diagnostic test is 100 percent accurate. Neonates who are siblings or close relatives of an affected individual have a 25 percent risk of having the condition themselves. They are, therefore, not part of the “general population” for whom newborn screening is designed. For any infant with a positive family history, providers should contact appropriate consultant specialists, ideally prenatally, or immediately at birth, to determine the proper diagnostic tests and proper timing of those tests and whether supportive therapy is needed.

SCREENING SIBLINGS OR AN INFANT OLDER THAN 6 MONTHS OF AGE:

The OSPHL does not screen infants older than 6 months due to a lack of age appropriate cutoffs. Infants and children older than 6 months can be “screened” using a filter paper specimen, but it should be sent to a diagnostic laboratory with age-appropriate cutoffs. (See [page 15](#) for information on screening older infants and children.)

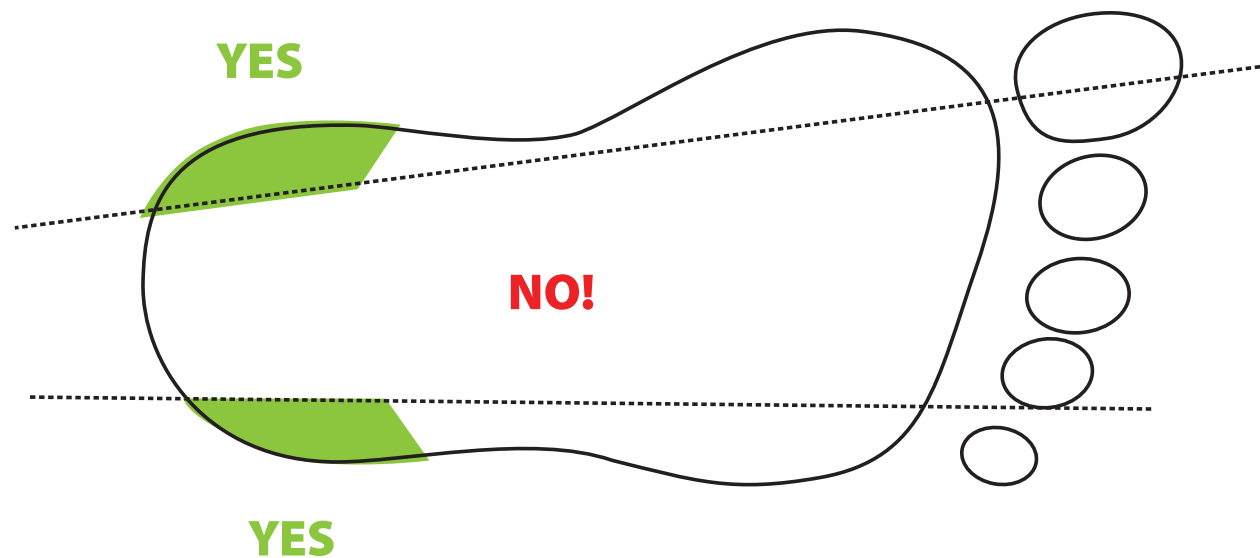
1. To prevent specimen contamination, do not touch any part of the filter paper circles before, during or after collection. Multiple agents can contaminate filter paper (see Unsatisfactory Specimens chart on [page 22](#)).
2. Identify infant and match with correct screening kit. Make sure to select the correct kit part (1, 2 or 3) depending on which specimen is being collected.
3. Complete all demographic data before proceeding to collection.
4. Observe universal precautions.
5. Capillary blood obtained from a heel lance is the preferred specimen. Cord blood is not a satisfactory specimen as the infant's biochemistry will not be reflected. Specimens obtained from peripheral or central lines are acceptable if they are flushed of parenteral nutrition or antibiotics. Blood from an intravenous stick is acceptable as long as it does not clot and can be applied to the filter paper directly.
6. It is essential to open a capillary bed to obtain sufficient blood. The most effective method is to use scalpel bladed lancets manufactured specifically for heelsticks in infants. Pointed lancets are painful to the infant and make a hole rather than a small slit, greatly reducing blood flow. Under no circumstances should a lancet longer than 2.0 mm be used on infants weighing less than 2,500 grams.
7. As per your institution's protocol, heat infant's foot if necessary in warm water, towel, or chemical pack. Heat source should not exceed 42 degrees centigrade and should not be left in contact with skin for a prolonged period.
8. Select a lance site on the infant's heel (see [diagram](#)), cleanse with alcohol and air dry. Hold infant's limb lower than heart.
9. Lance the heel with the sterile scalpel bladed lancet. Wipe away the first drop of blood to remove tissue fluids. Do not milk the heel. If blood flow is insufficient it is better to stop and re-lance the heel.
10. Allow sufficient blood to collect on the heel to fill each circle by a single application of blood to the filter paper. Do not use capillary tubes or other collection devices. Apply blood only to one side of the filter paper (it doesn't matter which side is used). Blood should soak all the way through the filter paper so that the blood spots look similar on both sides. Complete, even saturation of the entire circle is essential for accurate testing. Neatness doesn't count.
11. It is important not to superimpose blood drops on top of each other. Let each drop touch the paper about 1/8 inch away from each other. This may prevent layering and uneven saturation, one cause of false results.
12. Collect the blood in all four circles. A minimum of three circles is necessary to complete the screening battery. If there are problems with sufficient blood flow, it is better to fill three circles completely than to fill four circles inadequately (see #9 above).
13. After circles are filled, the foot should be elevated above the heart and a sterile gauze pad or cotton swab pressed against the puncture site until the bleeding stops. Bandages should be avoided as they may irritate sensitive skin.
14. Air dry specimens at room temperature for 2–4 hours in a horizontal position with the blood spots exposed. (A CD holder works well.) Hanging wet specimens will cause heavier red cells to migrate to the dependent end of the circle resulting in uneven saturation.
15. Do not expose the specimen to heat or humidity at any time. Do not dry on a heater, in a microwave, with a hair dryer or in sunlight. Do not place in plastic bags, leave in a hot mailbox or in a hot car; proteins and enzymes will be destroyed. Ensure that the specimen is completely dry before mailing. In hot weather, desiccant packets may be added to reduce humidity during transit.
16. Do not batch specimens collected over several days as infants affected with emergent disorders may die before results can be made available. Specimens can be sent in the same package, but there must be a daily mail or courier pick up for all specimens.
17. Insert dried specimens into an envelope (do not use plastic), seal and mail within 4–12 hours of collection and no later than 24 hours after collection. Weekend and holiday specimens should be stored at room temperature and sent by overnight mail or courier at the earliest opportunity. All specimens should be sent by first class or overnight mail or by courier. Specimens should be received by the OSPHL within 12–48 hours of collection.

18. Specimens should be documented as sent. If by courier, a packing list should be kept and the courier should sign for pick up and delivery of specimens. This step protects the hospital from liability in the event the specimen is lost in transit.

* These recommendations conform to CLSI publication LA4-A5. See [page 28](#).

Recommendation for heel puncture site in newborns

Perform punctures on the most medial or most lateral portion of the plantar surface of the heel (see diagram at right).



A full-color chart illustrating proper specimen collection, "Neonatal Screening Blood Specimen Collection and Handling Procedure," may be obtained at no charge from Whatman, part of GE Healthcare, E-mail: info@whatman.com Website: www.whatman.com/NeonatalScreeningProducts.aspx

Newborn screening laboratories receive many specimens that are unacceptable for testing. If the specimen is improperly collected, the accuracy of the screening test results is compromised, and the laboratory must reject

them. This incorrect procedure then requires that the submitter locate the infant and repeat the collection procedure, which delays the screening of the newborn. The following table outlines the most common errors in specimen collection.

Consult the New Mexico Newborn Screening Program for additional information and assistance with specimen collection.

Unsatisfactory specimen	Possible causes
<p>Uneven saturation: Blood spot appears layered and/or scratched or abraded.</p>	<ul style="list-style-type: none"> • Application with a capillary tube or needled syringe. • Applying blood to both sides of the filter paper. • Touching the filter paper with fingers or gloves. (Sweat and oils from fingers or powder/residue from gloves affect absorbency of filter paper.) • Layering several blood drops on top of each other. • Hanging filter paper to dry. • Compression of the filter paper.
<p>Insufficient blood (QNS): Blood spots do not look the same from both sides of the filter paper.</p>	<ul style="list-style-type: none"> • Failing to open a large enough capillary bed resulting in insufficient blood flow from the infant's heel to allow complete absorbency through to the second side. • Removing the filter paper before blood has completely soaked through to the second side.
<p>Contaminated: Blood spots appear to be contaminated.</p>	<ul style="list-style-type: none"> • Not wiping the alcohol from the puncture site before lancing the skin. • Not wiping away the first drop of blood to collect on the heel. • Allowing the filter paper to come in contact with alcohol, formula, bodily fluids, water, etc., before or after the blood specimen collection. • Squeezing or milking the area around the puncture site may cause contamination or dilution with tissue fluids. • Using a non-isopropyl alcohol swab (betadine or non-sting skin prep swabs) may destroy the proteins in the blood, alter absorbency or give false positive/negative results.
<p>Blood received wet: Blood spots appear to be "wet" when received.</p>	<ul style="list-style-type: none"> • Mailing the specimen before drying a minimum of two hours. • Placing in a plastic bag even after minimum drying time.
<p>Pale blood: Blood spots appear very pale or "washed out" in color.</p>	<ul style="list-style-type: none"> • Low hematocrit in a normal newborn. • Infant is very ill or of very low birth weight. • Contamination of the filter paper before or after application of the blood.
<p>Specimen too old: Specimen received in the laboratory more than 14 days after collection date.</p>	<ul style="list-style-type: none"> • Specimen was not mailed within 24 hours after collection.

Before discharge, hospital and birth unit personnel may be designated and listed on the request slip as the physician-of-record. In the event of an abnormal test result, the screening laboratory will refer to the physician-of-record although the infant is no longer under his or her care and may not even be known to him or her. Responsibility for follow-up remains with the physician-of-record until another practitioner actively accepts it. It is essential to list the practitioner who will be providing direct care after discharge.

Web-Rad

Results for all infants born in your facility or under care in your practice can now be accessed online through the OSPHL's website. Contact New Mexico Newborn Screening Program by phone (505-476-8668) or e-mail to sign up and obtain a user ID and password.

Normal results

Normal results are mailed daily to hospitals and to the physician-of-record. The complete test battery is usually completed in 2–10 working days after receipt by the laboratory.

“Significant” abnormal results

All results considered urgent are reported to the medical consultants who will phone the submitting hospital or practitioner with recommendations for further action. Such action is followed by mail or fax confirmation.

Other abnormal and repeats

Lesser abnormalities or inadequate samples are reported immediately by phone or fax to the submitting hospital and/or practitioner with a request for retesting.

It is the practitioner's responsibility to ensure that all infants with abnormal results are retested; however all such infants are also tracked by the laboratory and/or the medical consultants until a resolution or diagnosis is confirmed.

State health agencies are notified for assistance when there are problems in obtaining repeat tests for infants with abnormal results.

Practitioner responsibility for documentation

It is the responsibility of the practitioner to ensure every infant is tested and that a result is received and filed in the medical record. Practitioners should know the screening status of every infant in their care, regardless of age. Specific care should be paid to infants/children adopted from overseas as not all countries have newborn screening programs.

Specimen collection must be documented in the infant's chart and if preferred in a separate logbook. Information should include name of infant, hospital ID number, screening kit ID number, date collected, date mailed and the name of the person who collected the specimen. When screening results are returned to the submitter they should be noted in the logbook and the report filed in the medical records. Community practitioners must also ensure that the second specimen is obtained at the appropriate time and that documentation is completed.

In the event the results of an infant's screening tests are not received from the screening laboratory within two weeks of collection, the hospital and practitioner should assume responsibility for follow-up. If requested the New Mexico Newborn Screening Program can become involved. We recommend the following procedure:

New Mexico Newborn Screening Program at 505-478-8868 or WebRad to determine if specimen was received and to request a report to be mailed or faxed.

1. If the specimen was not received, it must be presumed lost. Notify the infant's private physician, local health department nurse and/or parents by phone and letter that the specimen may have been lost and that another should be obtained without delay.
2. Document these actions in the infant's medical record.
3. Request a copy of the repeated screening results be sent to your facility for the medical record.
4. If these steps do not result in the infant being screened, notify Brenda Romero, RN, BSN, 505-476-8857 or Carla Ortiz, RN, BSN, 505-476-8858, the infant's health care provider and consider a public health nurse referral.

Infants who are never tested

Mandatory state screening laws in the United States were passed in the 1960s not because parents were opposed to screening, but because hospitals and practitioners were slow to provide screening services. While screening programs are now universal in the United States, it is estimated that approximately 1–2 percent of births are not screened either because of parental refusal or practitioner oversight or omission. For every 1 percent of newborns not screened in the United States, approximately 45–50 infants will be missed each year. These infants represent a major medical and legal liability to the program and to practitioners involved in their care. The legal awards for missed cases have been as high as \$30 million per case. Hospitals must develop a fail-safe system to ensure screening of every infant before discharge. In addition, community practitioners must pay special attention to older infants not born in the United States (i.e., adopted and/or migrant), infants born at home or older infants or children with symptoms of one of these conditions.

Parents' refusal to have the infant tested

See [page 13](#) for guidelines, and [page 33](#) for the New Mexico Waiver Form and instructions on use.

Common misconceptions of practitioners

Failure to test an infant is often due to misconceptions about the program or the tests.

For example:

- **The diseases are so rare practitioners may advise parents not to have screening done.**

FACT: NBS identifies 1:1,000 infants with one of the conditions included on the screening panel. Nationally this represents 5,000 infants/year who would otherwise die or become irreversibly harmed by a late or missed diagnosis. In New Mexico, 30–45 infants are identified each year.

- **Practitioners may believe the first test is of no value if obtained before 24–48 hours of age or before the infant has ingested protein or milk.**

FACT: 90 percent of affected infants have abnormal results on the first test regardless of age or food ingestion. The ability to identify infants relates to a combination of the severity of their genetic disorder, physiologic and environmental factors, the quality of their screening specimen and the rapidity of the entire screening system to find them before they become symptomatic. There is nothing magic about a specific age cutoff as each disorder has its own “best screening window” and they are all different. Dietary intake does make a difference in galactosemia, in that a galactosemic infant on a soy-based or other non-lactose formula would not be ingesting galactose and may have false negative results although newer laboratory assays make that less likely. Infants who are well fed may have normal acylcarnitines for fatty acid disorders. Dietary information is helpful to evaluate the significance of certain abnormal results.

- **Practitioners may believe the second screen is unnecessary.**

FACT: Approximately 11 states mandate a second screen for every infant and virtually all states recommend it if the first screen is drawn before 24 hours of age. In Oregon and other states with repeat screens, 10 percent of all infants affected are routinely found only on the second screen.

Approximately four of the conditions on the screening panel may take a week or more to manifest themselves, long after an infant has been discharged and screened the first time. The efficacy of a second screen is controversial and under study by the U.S. Centers for Disease Control and Prevention.

- **Practitioners may believe the second screen is unnecessary if the first screen is collected when the infant is 5–7 days of age.**

FACT: More than 20 conditions on the screening panel can kill or maim in the first week to 10 days of life. To delay screening would mean almost certain death or disability for these infants and a test at 5–7 days is too early to pick up many of the later onset disorders. A test at the end of the first week of life is better than no test, but is probably the worst time to collect it in terms of saving infant's lives and mental capacity.

- **Some practitioners believe the pain of specimen collection is so great for the infant that screening is not “worth it,” or that the infant will suffer permanent psychological damage.**

FACT: The pain of a heel stick can be minimized if not eliminated by using a scalpel bladed lancet device and by feeding the infant a small amount of sucrose water or breast milk before and during

the procedure. Many families can attest that it is far more painful to have the infant die or to spend one's life permanently damaged because a few drops of blood were not collected at birth.

- **Practitioners may believe newborn screening is “just a piece of paperwork” to be gotten out of the way.**

FACT: Newborn screening represents one of the most successful public health programs ever undertaken in terms of prevention and cost savings, surpassing even immunizations. It is true that most programs do not do enough to alert practitioners to their importance and value to the screening process and to the number of infants identified.

- **Some practitioners tell parents that newborn screening is a test for “mental retardation.”**

FACT: Newborn screening tests for certain conditions that in some cases can lead to mental retardation. It is by no means a test for all sources of mental retardation and a normal screening result does not mean an infant will not be retarded due to other causes.

- **Many practitioners use the antiquated term “PKU test” which implies to parents that PKU is the only condition screened for.**

FACT: More than 30 separate disorders (including PKU) can now be screened for in the newborn period. PKU has not been the only disorder on most screening batteries since the mid-1970s when hypothyroidism was added. Newborn screening for PKU, galactose and leucine started in Hawai'i in 1968. The correct term is newborn screening (NBS).

Timing of the tests

In New Mexico in 2006, 85 percent of all first samples were obtained before 48 hours of age, and 88 percent of infants were screened twice. Most infants were initially screened between 24–48 hours of age, providing the best chance to pick up early onset disorders. Only a small number (1.57 percent) were screened at five days or later.

Specimen inadequacy

For the last couple of years, unsatisfactory specimens, particularly uneven saturation, have been slightly decreasing in the state and in 2010 represented 1.1 percent of all first specimens in New Mexico. These specimens generate an automatic request for a retest and delay screening, exposing affected infants to unnecessary delay in treatment and possible death or harm from their conditions.

The continued increase in unsatisfactory specimens is due to a number of factors. The technology used in the OSPHL is very sensitive and requires a precise amount of blood to give reliable and correct results. As a result, the OSPHL staff has to examine specimens more carefully. In the hospitals and birth centers many are still using capillary tubes or needles to collect specimens which is the primary reason for uneven saturation.

New, inexperienced or temporary staff in hospitals are more likely to collect unsatisfactory specimens as hospitals cope with nursing shortages. Educational efforts over the past two years have been focused on specimen collection as it has been recognized as a large problem. In spite of working together, the unsatisfactory rate for the region has just slightly decreased.

Hospital nurse managers and laboratory managers are notified of inadequate specimen by e-mail. Practitioners are notified by fax if the specimen is quantity not sufficient or contaminated.

Inadequate demographic information

In New Mexico 1.5 percent of specimens are missing key patient data. For example, the specimen does not list the infant's time of birth, or it is unreadable. In the event of an abnormal result, these specimens are difficult and time consuming to match to the correct infant, especially in large facilities. The most common cause for unreadable specimens is illegible handwriting. It is important to write clearly and neatly. Data which are critical include: name, birth date/hour, sample date/hour, feeding status, mother's name, and practitioner's name.

Problems related to specimen transport to the laboratory

All specimens should be transported as soon as they are dry and no later than 24 hours after collection. The screening laboratory should receive them within 24–48 hours and no later than five days after collection. In 2010, New Mexico's specimens taking longer than five days to reach the laboratory presents 1.5 percent of all specimens.

While some are due to unavoidable postal delays such as holidays, most are caused by failure to mail the samples promptly. Samples may be delayed because of sluggish in-house mail, inefficient courier services or simple forgetfulness, but perhaps the most dangerous practice is “batch mailing,” when samples are held up to a week so postage costs can be reduced.

Specimens collected on Saturday, Sunday or Monday holidays are best stored in a cool room and sent express mail at the first opportunity as the Oregon State Public Health Laboratory is not open on weekends or holidays.

The importance of early sample collection and prompt transit is illustrated by the fact that infants with galactosemia, organic acidemias and fatty acid oxidation disorders may die within a week or two of birth. Enzyme activity and hemoglobin may be destroyed or diminished in specimens which are older than 10 days or which have been exposed to heat and humidity.

The charge for testing New Mexico infants includes a specific amount for educational activities to improve the quality of the screening practices within the state. The educational activities include a quality assurance surveillance program, educational sessions at your facility regarding any or all aspects of screening and comprehensive review of your facility's screening system by the education coordinator/consultant. In addition, educational materials are provided to all practitioners and parents. These materials include this manual, online tutorials, parent brochures and disease fact sheets. All of the educational services are available at NO CHARGE to your facility. Additional educational videotapes and/or DVDs listed below are approved by the New Mexico Newborn Screening Program and can be purchased

by individuals or facilities. Newborn screening is changing rapidly and will continue to do so in the foreseeable future. Recommendations a few years ago may be obsolete today. Practitioners moving into New Mexico or one of the regional states must reorient themselves to newborn screening rules and regulations that pertain to that state. While states are making an effort to develop consensus about screening recommendations, there is still a lot of variation from program to program and practitioners must be aware of those variations.

Screening practice surveillance

In an effort to assist hospitals, birth facilities and individual practitioners, the laboratory provides a quality assurance program that monitors some screening practices that can be ascertained from the screening cards (transit time, inadequate specimens, demographics omissions and timing errors). Screening Practice Profiles are provided on a quarterly basis to hospitals and birth facilities in New Mexico. A 2010 summary of the screening practices for New Mexico is shown below.

Screening practice profile 1st specimens: New Mexico summary 2010		
Number of specimens/month	2,179	RANGE (1,956–2,548)
Percent error free	92.57%	(89.77–94.57)
Error profile		
Transit delays	3.5%	(1.57–7.29)
Timing errors	0.81%	(0.20–1.24)
Inadequate specimens	2.14%	(0.80–3.89)
Demographic errors	2.1%	(1.39–3.24)

Additional education resources**CLINICAL AND LABORATORY STANDARDS INSTITUTE***

940 W. VALLEY ROAD, SUITE 1400
WAYNE, PA 19087-1898 USA
FAX: 1-610-688-0700
WWW.CLSI.ORG

LA04-A3-V (DVD)**Making a Difference Through Newborn Screening: Blood Collection on Filter Paper (PAL format)**

This DVD provides a visualization of each step in the blood specimen collection process and depicts the standard of practice, as defined by the CLSI consensus process, for collecting specimens on filter paper. It explains how to select and prepare the safest puncture site; choose the appropriate equipment; puncture the skin and apply blood to filter paper; care for the puncture site; identify and verify a valid specimen; and handle and mail the specimen to the laboratory. LA4-A4 accompanies the videotape along with laminated summary sheets. (25 minutes). Member price: \$ 125.00; Non-member price: \$ 250.00; e-mail: customerService@clsi.org

*Many hospitals are members of CLSI and employees can get the membership rates.

LA4-A5 (paper document or electronic document) Blood Collection on Filter Paper for Newborn Screening Programs; approved standard – Fifth Edition

This document addresses the issues associated with specimen collection, the filter paper collection device, and the transfer of blood onto filter paper, and provides uniform techniques for collecting the best possible specimen for use in newborn screening programs. Member price: \$ 75.00
Non-member price: \$ 150.00

LA-A5-QG Quick Guides: Laminated sheets

Specimen Collection for Newborn Screening showing proper collection based on LA4-A5 and Simple Spot Check, Sample Quality for Newborn Screening showing examples of inadequate specimens and causes. (Set) Member price: \$20.00; Non-member price: \$40.00

I/LA31-A Newborn Screening for Preterm, Low Birth Weight and Sick Newborns; Approved Guideline.

This document outlines the recommended protocols for screening preterm, sick or low birth weight infants for hearing loss and disorders detectable through dried blood spot testing. Member price: \$60.00; Non-member price: \$120.00

Blood Specimen Collection and Handling (poster): Demonstration in words and pictures, suitable for hanging in specimen collection area. Available at no charge from: Whatman; 200 Park Ave, Suite 210; Florham Park, New Jersey 07932; Phone: 973-245-8300 or toll free 1-800-whatman; Fax: 973-245-8301; Website: www.whatman.com/NeonatalScreeningProducts.aspx; E-mail: info@whatman.com.

Simple Spot Check (poster): Demonstration with words and pictures examples of adequate and inadequate blood spots. Suitable for hanging in specimen collection area. Available at no charge from: Whatman; 200 Park Ave, Suite 210; Florham Park, New Jersey 07932; Phone: 973-245-8300 or toll free 1-800-whatman; Fax: 973-245-8301; Website: www.whatman.com/NeonatalScreeningProducts.aspx; E-mail: info@whatman.com.

Practitioners' Manual and Condition Specific Fact Sheets can be downloaded online at:
http://nm.health.Org/PHD/nbs/index_shtml.

Birth facilities, health departments and community practitioners

1. **In-service or medical/nursing rounds** can be provided at your facility by newborn screening program staff and medical consultants. These presentations cover any (or all) aspects of the screening program and can be tailored to meet your needs and time frame. For example, physicians can request disease specific updates or hospital laboratory staff may want the specifics of specimen collection. It is recommended that facilities provide orientation sessions about newborn screening to all new employees, which should include review of this manual and have regular in-services from NBS personnel.
2. **Assistance with specific screening practice problems** is available from the NBS educator or program staff. The issues are usually single-issue problems, such as a large number of unsatisfactory specimens or specimens delayed in transit. These problems are generally handled by phone and/or e-mail and are readily solved.

Online tutorials regarding all aspects of the program are available at www.oregon.gov/DHS/ph/nbs/index.shtm. The tutorials are designed to be used for new employee orientation, yearly performance review and/or individual refreshers.

3. **Policy development and/or review.** We are available to assist administrators and/or practitioners in the drafting of sound screening policies and procedures for their facility or practice based on state laws, administrative rules as well as recommendations of the American Academy of Pediatrics and the Clinical Laboratory Standards Institute. It is recommended that all hospitals and birth centers have similar policies and procedures for NBS so that standards of care exist for all infants born in Oregon. A review of your policies can be done in conjunction with in-service sessions or by e-mail or phone.
4. **Newborn screening system review for hospitals.** This process entails the formation of an ad hoc Quality Assurance (QA) Committee for NBS and includes representation from QA or risk management, nursing, medicine, laboratory, medical records, transportation, courier service, prenatal education and in some cases, community practitioners as well as the NBS educator as a consultant and/or committee member. The purpose of the committee is to review the NBS system within a facility to ensure uniformity and best practices. It generally results in the rewriting of policies and procedures and re-education of all staff. This process is particularly useful for large facilities with a large number of employees and numerous hospital departments involved in NBS. Depending on the problems and the ease of implementing solutions, this process can take 4–12 months. The NBS Educator can attend meetings in person or by conference call.

For additional information or to schedule a session please contact:

Brenda Romero, RN, BSN
Newborn Screening
Children's Medical Services
2040 S. Pacheco Street
Santa Fe, NM 87505
505-476-8857
E-mail: brenda.romero@state.nm.us

Only a standardized, quality tested filter paper can be used for specimen submission (Whatman). Requests for kits must be made using a kit request form (see page 30) showing the quantity requested and must include a check for prepayment.

Orders and payment should be submitted to:

Children's Medical Services
Attn: Newborn Screening Program
2040 S. Pacheco Street
Santa Fe, NM 87505

Orders Faxed to:
Attn: Newborn Screening Program
505-476-8896

Please allow 2–3 weeks for preparation and shipping. Kit orders and specimens are not to be sent by collect mail. If the Institution wants the kits sent overnight, it is at the cost to the institution.

Type of kits

Hospitals, midwives and birthing facilities receive double kits with identical kit numbers, so that the first and second specimens can be matched easily. Health departments, clinics, and private practitioners may order double or single kits. Single kits should only be used when the second part of a double kit has been lost, damaged or infant is born out of state. Please note: all kits are precoded for the specific individual/facility; they must not be **loaned to or borrowed from** other facilities. Three-part kits are available only to NICU's.

To obtain uncoded kits in emergency situations, contact Brenda Romero, RN, BSN, 505-476-8857 or Carla Ortiz, RN, BSN, 505-476-8858.

Cost

Double kits (two specimens) and NICU kits (three specimens) are \$89.00 per kit. Single kits cost \$25.00.

Storage of filter paper kits

Store unused filter papers on their sides. The filter paper used for NBS is classified as a medical device. Filter paper can be compressed if stored lying flat with potential for other objects to be placed on top. Compressed filter paper will not absorb blood in a normal manner and will result in specimen rejection.

Cost of diagnostic tests for confirmation of abnormal screening results

When diagnostic quantitative tests are requested by the laboratory or by the medical consultant for full evaluation of an infant considered likely to have one of the disorders, the costs of performing these will be absorbed by the program if the family has no insurance and provided that the samples are properly handled and submitted to a laboratory approved by this program. Fees for tests which are not specifically requested or sent to other laboratories will not be reimbursed.

The program does not cover postage costs for any specimens.

The program does not pay for family studies.



**Children's Medical Services
Newborn Genetic Screening Program
REQUEST FOR NEWBORN SCREENING KITS**

1. Please fill out this form completely to ensure you will get the correct kits.
2. Fax this form back to : **Att: Newborn Screening Program**
Fax: (505)827-5995

3. Ph: **(505)476-8856** Your "Ship to" info:

ATTN: _____

FACILITY NAME _____ SUBMITTER CODE # _____

STREET ADDRESS _____
(NOT PO BOX)

CITY _____ STATE _____ ZIP CODE _____

TELEPHONE # (____) _____ PO # _____ (if available)
(send a copy if this is a new one)

ORDERED BY _____ Place Bar Code here: Verified _____

ORDER DATE _____

Number of Double Kits requested _____

(Allow 2 weeks for delivery)

Number of Single Kits requested _____

(Limit of 5 per order)

(Allow 2 weeks for delivery)

Number of 3 part kits requested _____
For NICU units only.

Place Bar Code here: Verified _____
(OSPHL Use Only)

May be obtained at any time - No Charge:

	Amount	Verified
Manila Envelopes	_____	_____
Striped Envelopes	_____	_____

(OSPHL USE ONLY)
KIT NUMBERS

DATE RECEIVED _____ REVIEWED BY _____
DATE MAILED _____ MAIL BY _____


Exemptions

No infant should be refused newborn screening because of the inability to pay.


Families who cannot afford testing may be referred to the New Mexico's Newborn Screening Program. The New Mexico Newborn Screening Program will review each case for financial assistance with Newborn Screening.

Parental refusal

In the event a parent refuses the testing, the program strongly urges practitioners to obtain an "Informed Dissent" signed by the parent, placed in the infant's medical record, and forward copies to primary care provider, the New Mexico Newborn Screening Program, and the infant's parents. .



NEW MEXICO
DEPARTMENT OF
HEALTH



New Mexico
Newborn Screening Program
Newborn Screening Test Refusal

Name of Infant	Hospital of Birth
Birth Date	Street Address
Medical Record Number	City/State/Zip

- 1) I have received the Department of Health brochure entitled New Mexico Newborn Screening Tests, concerning the newborn screening tests for metabolic, endocrine and hemoglobin disorders.
- 2) I have been informed and I understand that these tests are required by State Law for all infants born in New Mexico.
- 3) I have been informed and I understand that these test are given to detect these disorders as babies may look normal and symptoms may not appear for several weeks or months.
- 4) I have been informed and I understand that untreated, these conditions may cause permanent damage to my child, including serious mental retardation, growth failure and in some cases death.
- 5) I have discussed the testing requirements with _____ and I
Name of Health Professionalhave had explained, and I understand all the risks involved if these tests are not given to my child.
- 6) I have been informed and I understand the nature of the tests and how these tests are given.
- 7) I object to these tests and I do not want _____ tested
Name of Infantfor these conditions.
- 8) Would you share with us the reason why you chose not to have your baby screened?

My decision was freely made without force or encouragement by my doctor, hospital personnel, or state officials and I accept the legal responsibility for the consequences of this decision.

Signed _____ Relationship _____

Witnessed by _____ Date ____/____/____

<p>Original Infant's Medical Record</p>	<p>Copy NM Newborn Screening Program 2040 S. Pacheco St. Santa Fe, NM 87505</p>	<p>Copy Parent/Guardian</p>
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Date: 05/02/2006

Core Conditions

Cystic Fibrosis (CF)

CF Essentials

- **Incidence:** 1:3,500
- **Screening test:** Trypsinogen >60 meq/L on two filter paper specimens. (Trypsinogen is elevated in pancreatic insufficient neonates but disappears from the blood by ~2-3 months of age.)
- **Confirmatory test:** Sweat chloride test and/or DNA mutation analysis
- **Validity:** Approximately 5% of cases will be missed due to pancreatic sufficiency. All other cases should be abnormal on the first screen. Trypsinogen may be falsely abnormal in premature or sick infants.
- **Treatment:** Comprehensive care, enzyme and vitamin replacement, high calorie diet and pulmonary care
- **Outcome:** Early diagnosis decreases morbidity and need for hospitalization; improves growth and development; provides a pulmonary benefit to age 15; survival to third decade. Refer to pediatric pulmonologist.

Cystic fibrosis (CF) is a recessively inherited defect of the cystic fibrosis transmembrane conductance regulator (CFTR) protein. Over 1,000 mutations of the CFTR protein have been identified, but a single mutation ($\Delta F508$), accounts for two-thirds of all the mutations worldwide. The incidence of CF in the United States is approximately 1:4,500, being more frequent in non-Hispanic whites (1:4,000) and

less so in non-Hispanic blacks (1:15,000). Newborn screening for CF is currently done for all infants in our region.

Clinical features

Mutations in the CFTR gene alter the structure, function or production of the transmembrane chloride channel protein that is critical to the normal functioning of multiple organs. These include the lungs and upper respiratory track, pancreas, liver, sweat glands and genitourinary track.

The first symptom for 10–20 percent of infants with CF is meconium ileus, an intestinal obstruction that presents in the first few days of life. Other symptoms of CF develop over time.

For infants without meconium ileus, the first symptoms include recurrent cough, wheezing, abdominal pain, loose stools and/or failure to thrive. Pancreatic insufficiency is present in 95 percent of CF individuals, and can lead to severe nutritional deficiencies and malnutrition. Recent studies suggest severely malnourished CF patients can suffer cognitive impairment as well.^{7,8} Respiratory symptoms may be absent in the neonatal period but develop in most individuals by the end of the first year of life. Unfortunately most of the symptoms are not specific to CF and in the absence of newborn screening, meconium ileus or prenatal diagnosis, the average age at diagnosis is 14.5 months. Most patients suffer progressive lung damage. Survival has improved dramatically over the years and patients now live into their 30s. Like most inherited disorders there are milder variants with proportionally fewer symptoms and a longer course.

Causes of CF

CF is a recessively inherited defect in the CFTR protein. CFTR deficiency results in abnormal chloride transport and the formation of thick sticky mucus, which in turn leads to organ dysfunction and failure.

Laboratory tests

The screening test measures trypsinogen, an enzyme produced in the pancreas that is transiently elevated in the blood of pancreatic insufficient CF infants at birth. This enzyme is detected by immunoreactive trypsinogen testing (IRT) test obtained from neonatal dried blood spots.⁹

If the IRT is elevated on the initial screen and on an additional screen collected greater than seven days of age this should prompt diagnostic work up, clinical correlation or both.

There are several issues to keep in mind regarding elevated IRT tests:

- Elevated IRT is not diagnostic of CF. False positives occur and are found in about half of infants with high IRTs.
- Infants with meconium ileus may not have an elevated IRT, so this diagnosis should lead to definitive testing for CF regardless of the IRT result. All infants with meconium ileus, however, should have a newborn screening specimen collected even if CF is suspected, as they should be screened for the other conditions on the screening panel.
- About 5 percent of infants with CF, who are pancreatic sufficient, may not have an elevated IRT. Thus a normal IRT at birth does not completely rule out CF. Children with recurrent respiratory problems, failure to thrive, etc., may still need a CF workup and sweat chloride testing.

Confirmation

CF can be diagnosed by two different methods. The first symptom for 10–20 percent of infants with CF is meconium ileus, an intestinal obstruction that presents in the first few days of life. Other symptoms of CF develop over time. A chloride value in the sweat of >60 meq/L makes the diagnosis, while a value of <30 meq/L effectively rules out CF. For a minority of infants, chloride values will fall in an intermediate range (30–60 meq/L) and will need follow-up.

DNA mutation analysis of the CFTR gene is another diagnostic method; however this may be problematic in patients with atypical mutations. Approximately 70 percent of CF is caused by a single mutation, $\Delta F508$, but there are over 1,600 other mutations associated with CF, and most are not included in standard multi-array DNA analyses.^{10,11} Confirmation of two deleterious mutations confirm the diagnosis, but only one may indicate a carrier state or an affected individual with a private mutation on the second allele.

Treatment

Treatment aims to ensure adequate nutrition and growth by supplementing pancreatic enzymes and vitamins and providing a high calorie diet. Daily chest physiotherapy and medications are required by most patients to loosen secretions. People with CF need rapid treatment of any chest infection with antibiotics. Routine immunizations plus inoculation against the flu and pneumococcus are recommended to help prevent chest infections. Infants should be referred to a CF center.

Screening practice considerations

- CF infants with meconium ileus or who are pancreatic sufficient may have normal IRT levels.
- IRT levels in affected infants will decline and be in the normal range by 3 months. Older infants or children suspected to have CF should have a sweat chloride test.
- IRT may be falsely elevated in premature or sick infants.

The purpose of newborn screening is to identify infants at risk and in need of more definitive testing. As with any laboratory test, both false negative and false positive results are possible. Screening test results are insufficient information on which to base diagnosis or treatment.

Results	Likely causes	Actions
Two elevated IRTs on filter paper specimens	<ul style="list-style-type: none"> • Cystic fibrosis probable • Possible false positive 	NBS nurse faxes results. Medical consultant phones practitioner with follow-up recommendations

Congenital Adrenal Hyperplasia (CAH)

CAH Essentials

- **Neonatal emergency:** 3/4 will develop salt wasting crisis, which can be fatal, in the first week to month of life.
- **Incidence:** 1:12,000 newborns; 1:300 Alaskan Natives (Yupik Eskimo)
- **Screening test:** 17-OH-Progesterone
- **Validity:** 90% identified on 1st screen, 10% on 2nd screen
- **Causes:** 21-hydroxylase deficiency or other inborn error of cortisol synthesis; recessive inheritance
- **Treatment:** Hydrocortisone and mineralocorticoids
- **False positives:** Occur more frequently in premature, low birth weight or sick infants
- **Outcome:** Early detection and treatment can be lifesaving. Chromosome analysis in infants with ambiguous genitalia will prevent gender mis-assignment. Ultimate outcome depends on severity of defect, days to treatment and adherence. Refer to pediatric endocrinologist.

CAH is an inherited defect of cortisol synthesis. The adrenal gland cannot make cortisol and overproduces male hormones. Without cortisol, infants are at risk for adrenal crisis and may be unable to regulate salt and fluids, and can die. The most common disorder is 21-hydroxylase deficiency. The incidence is 1:12,000 live births. The incidence is 1:300 in certain Yupik Eskimo populations. CAH is screened for in all infants in our region.

Clinical features¹²

Infants may be symptomatic at birth. By 4 to 5 months gestation, diminished cortisol production stimulates the fetal pituitary gland to produce ACTH resulting in excessive adrenal androgens. The androgens virilize female external genitalia, but ovaries and uterus are unaffected. Male infants may have increased scrotal pigmentation or may be asymptomatic.

In 75 percent of cases, the 21-hydroxylase deficiency causes reduced production of mineralocorticoids. This reduction leads to a hypotensive, hyperkalemic, salt-losing crisis with rapid onset of adrenocortical failure within 7–28 days of birth, which can be fatal. In 25 percent of cases, the infant has a “non-salt losing” or “simple virilizing form.” If untreated, these children have mild postnatal virilization, rapid growth with advanced skeletal age, early puberty, and short stature as adults. In adulthood, there is hirsutism and acne. Women have irregular menses and infertility.

Causes of CAH

The term “congenital adrenal hyperplasia” or “adrenogenital syndrome” covers a group of disorders. All are due to an inborn error of steroid hormone synthesis, which blocks the production of cortisol. The low level of cortisol stimulates ACTH, causing adrenal hyperplasia and increased secretion of steroid precursors. Different enzyme defects block the metabolic pathway at different sites and result in different clinical features. There are variants to this disorder, which have later onset. All forms of CAH are inherited as autosomal recessive disorders.

Laboratory tests

Screening is based on an immunoassay for a precursor steroid, 17-hydroxyprogesterone (17-OHP). Affected infants have high levels of 17-OHP. Infants with milder disorders have intermediate levels. False positives may occur in preterm, low birth weight and sick infants.

Confirmation

Confirmation is by measurement of serum 17-OHP and if salt wasting is suspected, sodium, potassium and plasma renin activity. Chromosome analysis to confirm gender if genitalia are ambiguous.

Treatment

Infants should be treated with hydrocortisone and mineralocorticoids in consultation with a pediatric endocrinologist.

Screening practice considerations

- This disorder kills quickly and is a neonatal emergency. In both sexes, salt wasting and shock may develop rapidly within 7–28 days of birth. Collect specimens between 24–48 hours of life. Transport all specimens 4–12 hours after collection and no later than 24 hours.
- Female infants who are virilized or infants with ambiguous genitalia should be considered at risk for this condition, tested at birth and monitored for electrolyte abnormalities until the diagnosis is excluded.
- Male infants are not usually recognized at birth.
- About 10 percent of infants will be detected only on a second screen.^{13,14,15}

Results	Likely causes	Actions
>150 ng/mL if <24 hrs old >120 ng/mL if 1-10 days old >70 ng/mL if >10 days & BW <2500 g >100 ng/mL if <24 hrs old >60 ng/mL if 1-10 days old >50 ng/mL if >10 days & BW ≥2500 g	<ul style="list-style-type: none"> • CAH probable • False positive 	Neonatal emergency; NBS nurse faxes results. Medical consultant phones practitioner with follow-up recommendations.

The purpose of newborn screening is to identify infants at risk and in need of more definitive testing. As with any laboratory test, both false negative and false positive results are possible. Screening test results are insufficient information on which to base diagnosis or treatment.

Congenital Hypothyroidism

CH Essentials

- **Incidence:** 1:3,000 newborns
- **Screening test:** T4 (thyroxine) and TSH (thyroid stimulating hormone)
- **Validity:** 90% identified on 1st screen, 10% on 2nd screen
- **Causes:** Thyroid dysgenesis: 85%; hereditary inborn error of thyroid hormone biosynthesis: 15%
- **Treatment:** L-thyroxine normalize T4 by 2 weeks of age; TSH by 1 month
- **False positives:** Early collection within 24 hours of birth; premature or ill infants
- **Outcome:** Can be normal, but depends on severity of thyroid deficit, days to treatment and adherence to treatment. Infants with just a 2-week delay in reaching a serum T4 >10 ug/dL may have up to a 10 point drop in IQ.¹⁶

Congenital hypothyroidism (CH) occurs in infants who are born without the ability to produce adequate amounts of thyroid hormone. Thyroid hormone is important for normal function of all of the body's organs and is essential for normal brain development. The incidence of congenital hypothyroidism is 1:3,000. CH is more common in Hispanic and Native American populations (1:700–2,000). There is a 2:1 female/male ratio, explanation unknown. Infants with Down's syndrome have increased risk of CH (1:140 newborns).

Screening for congenital hypothyroidism is done for all infants in our region.

Clinical features¹⁷

Deficiency of thyroid hormone in an infant may result in mental retardation and other signs of brain damage if it is not diagnosed and corrected by 3–4 weeks of life. Many infants with CH may appear clinically normal before 3 months of age, by which time some brain damage has usually occurred. Laboratory test results are the only reliable means of diagnosing CH in the newborn.

When symptoms or signs are present, they may include prolonged neonatal jaundice, constipation, lethargy and poor muscle tone, feeding problems, a large tongue, puffy face, large fontanelles, distended abdomen and umbilical hernia. Approximately 10 percent of cases will have other congenital abnormalities, usually cardiac defects. Long-term neurologic damage includes mental retardation, ataxia, fine and gross motor delay, slow growth, speech disorders and hearing deficits in 20 percent. Since thyroid deficiency can occur at any age, normal tests in the newborn period do not exclude deficiency in an older infant or child.

Causes of congenital hypothyroidism

The most common causes are total or partial failure of the thyroid gland to develop (aplasia or hypoplasia), its development in an abnormal location (an ectopic gland) or a defect in thyroid hormone production (dysmorphogenesis). Less commonly, hypothyroidism is induced by medications (antithyroid drugs or excess iodine) in the mother, or maternal autoimmune thyroid

disease with transfer of a maternal antibody that blocks the fetal thyroid development.

Laboratory tests

The initial screening test is the T4 assay. Infants with T4 results of <10 percent are further tested by a screening TSH assay. Different combinations of results are possible; [see table on next page](#).

When the infant's physician is notified that screening results are abnormal, blood should be collected by venipuncture as soon as possible to confirm the abnormal screening results. In the case where the T4 is low and TSH is elevated, treatment can be started as soon as the serum is obtained, pending final confirmation. If the serum thyroid function tests confirm hypothyroidism, further diagnostic studies, such as a thyroid ultrasound examination or scan and X-ray to assess skeletal maturation, may be performed to determine the type, age of onset and severity of hypothyroidism. Generally, these studies do not change management and so are optional.

Thyroid function in premature infants

In premature infants, there is a physiological reduction in blood T4 levels; TSH levels are not elevated in this situation. These cases need special observation to ensure that the low T4 levels rise into the normal range as the infant matures, but this may take several weeks. Serum free T4 levels (by equilibrium dialysis method) are often normal. There is no consensus that these infants benefit from thyroid supplementation during this period.

Treatment

The American Academy of Pediatrics (AAP) recommends that infants be managed in consultation with a pediatric endocrinologist.¹⁸ Treatment of CH is effective if done correctly. L-tyroxine (brand or generic l-thyroxine), in pill form, is crushed, mixed with water or expressed breast milk and administered once daily. Currently, there are no FDA-approved liquid formulations. The recommended starting dose is 10–15 mcg/day of body weight daily, usually 37.5 mcg/day to 50 mcg/day. AAP recommendations for follow-up serum T4 (or free T4) and TSH are as follows:

- Initiation of treatment and 2–4 weeks later
- Every 1–2 months in the first 6 months
- Every 3–4 months from 6 months–3 years of age
- Every 6–12 months from age 3–end of growth period

Treatment Goals: Maintain serum T4 or free T4 in the upper half of the normal range (10–16 µg/dL for T4 or 1.2–2.4 ng/dL for free T4 [normal range may vary with assay]), and TSH normalized (<10 µIU/mL). Clinical evaluations can occur less frequently. As infants grow, the dose of thyroxine is increased. Periodic developmental testing should be done on all patients. If treatment is started early and thyroid levels are monitored closely, development remains normal.

Screening practice considerations

- Hypothyroidism is the most common disorder detected by the program.
- Ninety percent of hypothyroid infants are detected on the first specimen; in 10 percent of cases, hypothyroidism develops in the weeks after birth and is detected on a second screening test as production of thyroid hormone decreases after birth.^{18,19,20}

- Some infants (usually pre-term) will manifest a delayed rise in TSH, and so are also detected on the routine second or third screening test. Practitioners therefore must remain alert to clinical symptoms in premature and older infants despite normal initial screening.
- False positive results may occur if the specimen is collected within the first few hours after birth, as the TSH rises in response to the extra-uterine environment.
- Topical iodine use on the infant or a mother who is breastfeeding may cause transient hypothyroidism.

The purpose of newborn screening is to identify infants at risk and in need of more definitive testing. As with any laboratory test, both false negative and false positive results are possible. Screening test results are insufficient information on which to base diagnosis or treatment.

Results	Likely causes	Actions
T4 low/TSH elevated	<ul style="list-style-type: none"> • Hypothyroidism probable • False positive 	NBS nurse faxes results. Medical consultant phones practitioner with follow-up recommendations.
T4 low/TSH > 100 and ≤200 µIU/mL, 0–11 hrs.	<ul style="list-style-type: none"> • Prematurity hypothyroidism possible • False positive 	NWRNSP contacts practitioner by FAX and by mail requesting further testing.
T4 low/TSH normal (on two specimens unless premature)	<ul style="list-style-type: none"> • Thyroid binding globulin (TBG) deficiency • False positive • Pituitary gland problem with secondary hypothyroidism • Prematurity 	NWRNSP contacts practitioner by mail requesting further testing.

Sickle Cell Disease and other Hemoglobinopathies

Sickle Cell Disease Essentials

- **Incidence:** 1:5,000 births; 1:400 African Americans
- **Screening test:** Isoelectric focusing (IEF), high performance liquid chromatography (HPLC)
- **Confirmatory tests:** IEF and/or HPLC
- **Validity:** 100% found on 1st screen (unless transfused)
- **Treatment:** Comprehensive care, prophylactic penicillin, immunizations, and empiric treatment of febrile episodes. Refer to pediatric hematologist.
- **Outcome:** Screening prevents death from sepsis in most infants. Long-term outcome depends on the severity of the hemoglobinopathy and response to treatment.

The primary goal of hemoglobinopathy screening is diagnosis of significant sickling hemoglobinopathies in the neonatal period, before symptoms occur. Newborn diagnosis of sickle cell disease, if coupled with family education and centralized comprehensive care, can markedly lower morbidity and mortality.²¹

Homozygous sickle cell disease (SCD) occurs when the recessive gene for hemoglobin S, sickle hemoglobin, is inherited from both parents. The term “clinically significant sickling syndrome” also includes conditions resulting from inheritance of one gene for hemoglobin S and certain other

unusual hemoglobins, such as beta thalassemia or hemoglobin C. These doubly heterozygous conditions tend to be less severe than SCD, though all are capable of producing severe complications. The incidence of SCD in the African American population is 1:400, but also occurs at a lower frequency among all other ethnic groups. The disease incidence in a population depends on the population's ethnic composition. Screening for hemoglobinopathies is done for all infants in our region.

Clinical features

Sickle syndromes are systemic diseases and may affect any organ. They are characterized clinically by chronic hemolysis, intermittent vaso-occlusion and marked variability. Some patients experience unremitting complications, others lead a full and productive life. While newborns are generally asymptomatic, early manifestations in infancy or early childhood can be life-threatening and include overwhelming infection due to splenic dysfunction, splenic sequestration crisis, and aplastic crisis with profound anemia. Prior to newborn diagnosis and preventive care, mortality in the United States was 8–30 percent in the first three years of life. Some important complications include vaso-occlusive pain syndromes, osteomyelitis, acute chest syndrome, stroke, priapism, pyelonephritis, gallstones, skin ulcers, retinopathy and decreased life expectancy.

Other significant hemoglobinopathies are less common and even more variable. Their manifestations range from very mild chronic hemolysis to severe dyserythropoiesis requiring a lifetime of transfusion support. Early detection of these less common conditions, however, may prevent unnecessary diagnostic and therapeutic intervention.

Laboratory 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). If a hemoglobin abnormality is detected on the first filter paper sample, the second filter paper sample is also analyzed by IEF and HPLC. Thus, each hemoglobin abnormality is verified four times, using two different techniques on two different samples. Solubility tests (Sickle-dex, Sickle-prep, etc.) are never appropriate in infancy and should not be used to confirm screening results.

Treatment

Infants with significant hemoglobinopathies should have a primary care provider and receive periodic evaluation in a comprehensive care setting. Therapy begins with education of caregivers and includes prophylactic penicillin, prompt evaluation and empirical treatment of any febrile illness, and immunizations including those for encapsulated bacteria. Close attention is necessary for the common problems of poor growth, recurrent pain and febrile illnesses. Organ-specific complications, sedation and general anesthesia require special attention. Other treatments, including the use of blood products and investigational therapies depend on clinical course.

Carrier detection makes hemoglobin screening different

This is the only newborn screening test that regularly identifies carriers (heterozygotes) as well as those affected by a given disease. In fact, many

more carriers than disease states are identified for all hemoglobinopathies. If both parents are carriers of an autosomal recessive genetic trait, the risk of any infant of that couple being homozygous is 1:4. While the best way to handle this genetic information has yet to be agreed upon, several principles are currently operative:

1. The family is entitled to the information and it is private.
2. If both parents of a SCD carrier infant are African American, they have at least a 2 percent risk of having a subsequent child with SCD, because at least one of them is now known to be a carrier. The family should be offered testing and genetic counseling. If the family declines participation, this should be documented.
3. The abnormal screening results may need to be confirmed using a liquid blood specimen. The medical consultant for hemoglobinopathy screening is available for assistance.

The purpose of newborn screening is to identify infants at risk and in need of more definitive testing. As with any laboratory test, both false negative and false positive results are possible. Screening test results are insufficient information on which to base diagnosis or treatment.

Screening practice considerations

- Newborn screening for hemoglobinopathies is not done on the second specimen unless an abnormality has been identified on the first specimen. It is crucial to use the first kit for the first test; the cards are not interchangeable.
- Transfusion of red blood cells prior to drawing the newborn screening specimen will invalidate the hemoglobinopathy test. Obtain a specimen before any transfusion.

- Some hemoglobinopathies, particularly the thalassemias, are not reliably detected through newborn screening and a normal screening result does not eliminate the possibility that a patient has a hemoglobinopathy. Further testing or consultation should be sought if indicated by clinical suspicion.

Results	Likely causes	Actions
FS (absence of A)	Sickle cell disease or Sickle beta thalassemia	NBS nurse faxes results. Medical consultant phones practitioner with follow-up recommendations.
FSC (absence of A)	Sickle hemoglobin SC disease	NBS nurse faxes results. Medical consultant phones practitioner with follow-up recommendations.
FC (absence of A)	Homozygous C disease	NBS nurse faxes results. Medical consultant phones practitioner with follow-up recommendations.
FE (absence of A)	Homozygous hemoglobin E or Hemoglobin E-beta thalassemia	NBS nurse faxes results. Medical consultant phones practitioner with follow-up recommendations.
FAS	Sickle cell carrier or Sickle beta thalassemia or Sickle cell disease in transfused infant	NWRNSP will report by letter regarding test results and any other recommendations.
FAC	Hemoglobin C carrier Homozygous C disease in a transfused infant	NWRNSP will report by letter regarding test results and any other recommendations.
FA+slow band	Possible carrier for hemoglobin E, O, D, or G	NWRNSP will report by letter regarding test results and any other recommendations.
FA+fast band	Possible alpha thalassemia Bart's hemoglobin is a marker for alpha thalassemia	NWRNSP will report by letter regarding test results and any other recommendations.
F only	Premature infant or Beta thalassemia major	NWRNSP will report by letter regarding test results and any other recommendations.
Predominance of A	Transfused infant or Patient outside of neonatal age range	NWRNSP will report by letter regarding test results and any other recommendations.

Amino Acid Conditions: Hypermethioninemia

Homocystinuria

(cystathionine beta-synthase deficiency) *

Homocystinuria Essentials

- **Incidence:** 1:100,000
- **Screening test:** Methionine by MS/MS
- **Confirmatory tests:** Quantitative methionine, homocystine in blood and urine
- **Validity:** 20% 1st screen; 80% 2nd screen
- **Treatment:** Pyridoxine if responsive; if not responsive, low methionine diet with cysteine and betaine supplements
- **Outcome:** Excellent if treated early and adherence is good

The most common form of genetic homocystinuria is cystathionine beta-synthase deficiency (CBS). CBS is required for conversion of methionine to cysteine and deficiency results in the accumulation of homocystine, methionine and cysteine-homocystine disulfides in the blood and urine. Unfortunately, methionine rises slowly in affected infants and may not be detectable on specimens obtained in the first few days after birth. Homocystinuria is inherited as an autosomal recessive trait and occurs in approximately 1:100,000 births. Screening for homocystinuria is done for all infants in our region.

Clinical features ^{22,23}

Untreated patients appear normal at birth, but by the first or second year mental retardation may

be apparent, most will develop dislocation of the lenses and a marfanoid body habitus, osteoporosis, and ultimately thrombo-embolism may develop which can result in stroke and serious, permanent disabilities or death.

Methionine Adenosyltransferase (MAT) Deficiency

A number of infants in the United States, identified through newborn screening with persistently elevated methionine, have been shown to have MAT deficiency. All but one patient has been asymptomatic, with normal growth and development. This patient had demyelination of the brain, but it is not clear that this is a result of MAT deficiency or other causes.

Laboratory test

Elevation of methionine is detected by MS/MS; normal methionine levels are $\leq 80 \mu\text{M/L}$ first specimen and $\leq 100 \mu\text{M/L}$ on second specimen. Transient elevations of plasma methionine in the newborn are unusual unless the infant is premature,

has liver disease or is receiving IV amino acid preparations. (i.e., parenteral nutrition).

Treatment

Some patients will respond to pyridoxine in large doses (250–1,200 mg/day). For patients unresponsive or partially responsive to pyridoxine, a methionine restricted diet is supplemented with cysteine and betaine is usually effective. The outcome for treated patients is dependent on the age at diagnosis, adherence with therapy and severity of defect. For those with good compliance, outcome is normal.

Screening practice considerations

- Methionine rises slowly in affected infants, so that the first screening specimen may be normal; 80 percent of the homocystinuria patients detected in the NWRNSP have been found on routine second tests.
- Methionine may be elevated secondary to liver disease, prematurity or parenteral nutrition.

* Not all forms of hypermethioninemia or even all cases of CBS deficiency will be detected by MS/MS.

Results	Likely causes	Actions
>80 & $\leq 190 \mu\text{M/L}$ 1st NBS Methionine > 100 & $\leq 190 \mu\text{M/L}$ 2nd NBS	<ul style="list-style-type: none"> • Homocystinuria/MAT deficiency possible • Tyrosinemia, Type I, galactosemia • Liver disease • Parenteral nutrition • High protein diet • False positive 	NWRNSP requests repeat filter paper specimen by mail.
Methionine > 190 $\mu\text{M/L}$	<ul style="list-style-type: none"> • Homocystinuria/MAT deficiency probable • Tyrosinemia, Type I • Liver disease • Parenteral nutrition • High protein diet • False positive 	NBS nurse faxes results. Medical consultant phones practitioner with follow-up recommendations.

Phenylketonuria (PKU) and Hyperphenylalaninemia

Hyperphenylalaninemia Essentials

- **Incidence:** 1:13,000 births
- **Screening test:** Phenylalanine >190 $\mu\text{M/L}$ by MS/MS; phenylalanine/tyrosine ratio >3.0
- **Confirmatory tests:** Quantitative amino acids; bipterins in blood and urine
- **Validity:** >99% on 1st screen
- **Treatment:** Low phenylalanine diet; bipterin supplementation
- **Outcome:** Normal if treated early and adherence is good

Detection of elevated phenylalanine levels requires urgent follow-up. This disorder is due to a recessively inherited enzyme defect in which the body cannot use the amino acid phenylalanine properly. All other metabolic processes are intact, but phenylalanine, which comes from all dietary protein, accumulates in the blood to toxic levels. All forms of hyperphenylalaninemias from mild to severe and including bipterin defects are inherited as autosomal recessive disorders. Screening for hyperphenylalaninemias is done for all infants in our region.

Clinical features

Infants with PKU seem to be normal for many months; however, without treatment, severe mental retardation, seizures, eczema and other problems usually develop. In older untreated patients the skin and hair may be fair, the eyes may be blue and a mousey odor of the skin or urine is common. Untreated blood phenylalanine level is often over 1,200 $\mu\text{M/L}$ in infants with severe PKU. Overall, PKU occurs in about 1 in 10,000–15,000 Caucasian and Hispanic births and is less common in other races. Although severe mental deficiency usually occurs in untreated cases, occasional asymptomatic adults are found with normal or near normal intelligence, despite high phenylalanine levels.

Plasma phenylalanine is not detectably elevated in cord blood. It starts rising within 24 hours after birth and often reaches 1,200 $\mu\text{M/L}$ or more within a few days. The screening test is often abnormal within 24 hours and almost uniformly abnormal within 48 hours of birth.

The phenylalanine/tyrosine ratio is uniformly abnormal in true cases and can be used to differentiate false positive infants.

Variant forms of PKU (Hyperphenylalaninemia)

Several intermediate forms of hyperphenylalaninemia occur in which the plasma phenylalanine levels are lower than in classic PKU (180–1,200 $\mu\text{M/L}$). In these cases, mental retardation is variable and in the milder variants is completely absent. In infancy, these patients can mimic severe PKU, and for adult women the risk of maternal PKU syndrome increases in proportion to the plasma phenylalanine.

Some forms of hyperphenylalaninemia are caused by defects of the cofactor bipterin metabolism and blood phenylalanine levels are variable. These patients have progressive neurological damage with seizures and steady deterioration that becomes noticeable sometime between 6 and 20 months of age despite early treatment with a low phenylalanine diet. Definitive tests can differentiate these variant forms of PKU. In view of the severity of this group of diseases, all infants with persistently abnormal levels of phenylalanine must have testing by special blood and urine tests for bipterin abnormalities. Information regarding this testing is provided through the metabolic consultants.

Maternal PKU and Hyperphenylalaninemia

Women with significant hyperphenylalaninemia have an increased risk of miscarriage and their offspring (who usually do not have PKU) may have intra-uterine growth retardation that persists postnatally. More than 90 percent of infants of untreated mothers with classical PKU have microcephaly, mental retardation, and/or congenital heart defects. They have a transient elevation of phenylalanine (240–1,200 $\mu\text{M/L}$) that falls to normal within 24 hours. A screening test on the mothers of infants with transient hyperphenylalaninemia, particularly if the infant's sample was collected in the first 24 hours after birth, is recommended. A phenylalanine restricted diet begun prior to conception and during pregnancy can often prevent damage to the fetus. Most childbearing women today, if born in the United States, should have been screened as infants, so the chances of undiagnosed hyperphenylalaninemias are remote but still present.

Laboratory tests

PKU and hyperphenylalaninemia are detected using tandem mass spectrometry (MS/MS); the normal phenylalanine level is $\leq 190 \mu\text{M/L}$ and the phenylalanine/tyrosine ratio is ≤ 3.0 .

Treatment^{24,25,26,27}

With proper treatment, mental retardation is totally preventable. Treatment should be started as soon after birth as possible (preferably in the first week) in any infant recommended for treatment by the consultants and should be continued indefinitely. Frequent monitoring is required, especially in the first weeks, because variant forms of hyperphenylalaninemia may be indistinguishable from classic PKU and improper nutritional therapy can be fatal.

If treatment is not started for some weeks, the results are more variable and the IQ tends to be

lower. Patients whose treatment begins after 6 months are likely to remain mentally retarded. Older patients usually show little change in IQ with treatment, but a low phenylalanine diet may help to control serious behavior problems.

Screening practice considerations

- Detection may depend on the amount of protein ingested or endogenously produced by the infant, but most affected infants (90 percent) have abnormal results even in the first 24 hours of life regardless of intake. Those with milder forms of hyperphenylalaninemia require longer periods of feeding or catabolism to develop abnormal tests.
- Contamination of the filter paper with food or liquids containing NutraSweet® (Aspartame) may cause false positive results or an inadequate specimen.

Results	Likely causes	Actions
Phenylalanine $>190 \mu\text{M/L}$, Phe/Tyr >3.0	<ul style="list-style-type: none"> • PKU possible • Variants forms of PKU • Mother has PKU • False positive • Transient hyperphenylalaninemia 	NBS nurse faxes results. Medical consultant phones practitioner with follow-up recommendations.

The purpose of newborn screening is to identify infants at risk and in need of more definitive testing. As with any laboratory test, both false negative and false positive results are possible. Screening test results are insufficient information on which to base diagnosis or treatment.

Tyrosinemia, Type I, II and Transient ***Tyrosinemia Essentials**

- **Incidence:** 1:100,000 (Types I & II) (1:1,000 transient)
- **Screening test:** Tyrosine > 480 µM/L by MS/MS, Succinylacetone >1.5 µM/L
- **Confirmatory tests:** Succinylacetone, blood amino acids, enzyme and mutation analysis
- **Validity:** >99% on either screening test for Tyrosinemia Type I
- **Treatment:** Low protein phe/tyr diet, medications and possible liver transplant in type I; low phe/tyr diet in type II. Transient tyrosinemia resolves within a month or two of birth or Vitamin C supplements for a few days will shorten the time.
- **Outcome:**
Type I: NTBC stops progression of disease and allows normal growth and development. The long-term risk of liver adenomas is still unknown, prompting some families to opt for liver transplant.
Type II and Transient: Normal outcome

Elevated tyrosine may result from an inherited defect of tyrosine catabolism or, as in transient tyrosinemia, delayed maturation of liver enzymes or liver disease. Screening for tyrosinemias is done for all infants in our region.

Transient Tyrosinemia²⁸

Transient tyrosinemia of the newborn is common (1:1,000) and more common among Inuit and

Eskimo populations in Alaska. Transient tyrosinemia is thought to arise from delayed maturation of the liver enzyme, 4-hydroxyphenylpyruvic acid dehydrogenase (4HPPD), coupled with increased protein intake and/or occult ascorbic acid deficiency. Tyrosine levels may be quite high (>480 µM/L) peaking at 14 days of life and resolved by 1 month. Premature infants or those on parenteral nutrition may have prolonged hypertyrosinemia.

Clinical features

Transient tyrosinemia of the newborn may present with lethargy or decreased motor activity, but is usually a biochemical abnormality found in an otherwise normal newborn. Transient tyrosinemia is not associated with long-term sequelae, although this has not been systematically studied.

Treatment

Transient tyrosinemia, while probably benign, may in some cases be treated with protein restriction to 2g/kg/day and administration of ascorbic acid (50–200 mg/day orally for 5–7 days) to infants found to have transient tyrosine (after types I & II are excluded). If the infant is breastfeeding, ascorbic acid alone may be crushed, dissolved in water and administered orally. Ascorbic acid, a co-factor for 4HPPD, helps to increase the enzyme's activity which will resolve the hypertyrosinemia more quickly if there are concerns about the infant's status.

Hepatorenal Tyrosinemia, Type I²⁹

Tyrosinemia, type I or fumarylacetoacetate hydrolase (FAH) deficiency occurs in 1:100,000 births. Hepatorenal tyrosinemia is inherited as an autosomal recessive trait.

Clinical features

Tyrosinemia, type I causes severe liver and renal disease and peripheral nerve damage. Presentation in infancy includes vomiting, lethargy, diarrhea and failure to thrive. Liver disease with hepatomegaly, hypoproteinemia, hyperbilirubinemia, hypoglycemia and coagulopathy may be present. In an international survey of 108 patients, 13 percent (n=14) became symptomatic in the first two weeks of life and 36 percent (n=39) in the first two months. Renal proximal tubular dysfunction results in aminoaciduria, hyperphosphaturia and hypophosphotemic rickets. Untreated, death in infancy or childhood from acute liver failure, neurological crises, or hepatocellular carcinoma is usual.

Treatment

Therapy with oral NTBC [2-(nitro-4-trifluoromethylbenzoyl)-1-3-cyclohexanedione] blocks the formation of the toxic metabolites. NTBC is effective in preventing or halting liver and renal damage and averting acute neurological crises. Long-term ability of NTBC to prevent the development of hepatic carcinoma is yet unknown, but 4/11 patients on NTBC have developed adenomas in a recent study.²⁹ The ultimate treatment, liver transplantation, has been successful in many cases. Adjunct therapy with dietary restriction of phenylalanine and tyrosine as well as symptomatic treatment of clotting defects, rickets and proximal tubular losses may also be needed.

Occulocutaneous Tyrosinemia

Tyrosinemia, type II is caused by a deficiency of the enzyme tyrosine aminotransferase (TAT) and is inherited as an autosomal recessive trait. TAT deficiency is rare, with about 100 cases described

worldwide, although more infants may be identified as MS/MS screening continues to be implemented.³⁰

Clinical features^{29, 30}

TAT is manifested primarily in the eyes, the skin and the central nervous system. In the eyes, tyrosine crystals accumulate resulting in painful corneal erosions. Equally painful hyperkeratotic plaques develop on the plantar surfaces of hands, feet and digits. Symptoms usually develop in the first year of life, but have been present on the first day of life or not occur until adulthood. A variable degree of mental retardation is present in about 50 percent of cases.

Treatment

A diet restricting phenylalanine and tyrosine is effective in clearing and/or preventing ulcerations.

Laboratory tests

Tyrosinemia is detected using succinylacetone by MS/MS; the cutoff tyrosine level is ≤ 480 $\mu\text{M/L}$. Tyrosine levels may be elevated. There is considerable overlap in tyrosine levels between normal infants, those with transient tyrosinemia and affected infants, making the tyrosine level itself not very specific.

Clinical correlation, blood amino acids and urine succinylacetone are necessary to differentiate these cases. More sensitive and specific tests for succinylacetone are under development and these will improve NBS for tyrosinemia.³¹

* Not all cases of tyrosinemia will be detected by newborn screening.

Results	Likely causes	Actions
Tyrosine >680 $\mu\text{M/L}$ Succinylacetone <1.5 $\mu\text{M/L}$	<ul style="list-style-type: none"> • Transient tyrosinemia • Tyrosinemia possible • Liver disease • Parenteral nutrition • False positive 	NWRNSP requests repeat filter paper in 2-3 months by mail.
Tyrosine > 480 $\mu\text{M/L}$ and ≤ 680 $\mu\text{M/L}$ Succinylacetone <1.5 $\mu\text{M/L}$	<ul style="list-style-type: none"> • Transient tyrosinemia • Tyrosinemia possible • Liver disease • Parenteral nutrition • False positive 	NWRNSP requests repeat filter paper by mail.
Succinylacetone >1.5 $\mu\text{M/L}$	<ul style="list-style-type: none"> • Tyrosinemia Type I • False positive 	NBS nurse faxes results. Medical consultants phones practitioner with follow-up recommendations.

Screening practice considerations

- Tyrosine may be slow to rise in affected infants, making it more likely to be found on routine second testing. Practitioners must remain alert to the possibility of tyrosinemia in any infant with liver disease, corneal or keratotic lesions.

The purpose of newborn screening is to identify infants at risk and in need of more definitive testing. As with any laboratory test, both false negative and false positive results are possible. Screening test results are insufficient information on which to base diagnosis or treatment.

Fatty Acid Oxidation (FAO) Conditions

FAO Condition Essentials

- **Neonatal emergency:** Approximately 10% of infants with FAO disorders will die in the first few days after birth, generally before screening results are known.
- **Incidence:** 1:6,000 births
- **Screening test:** Acylcarnitines by MS/MS
- **Confirmatory tests:** Acylcarnitine profiles, enzyme assay and/or mutation analysis
- **Validity:** 90% on the 1st screen, 10% on the 2nd screen
- **Treatment:** Avoid fasting, low fat diet
- **Outcome:** Variable depending on the FAO. MCAD patients do well if caught early and episodes are prevented. Outcome for other FAOs is still unknown.

Mitochondrial beta-oxidation of fatty acids is crucially important in the body's ability to produce energy during fasting. In infants, a "fasting" state can be produced in as little as four hours. Fatty acids must be transported into the cytoplasm and then into the mitochondria for oxidation; carnitine is required for these transport steps. Once in the mitochondria, fatty acid chains 4-18 carbons in length must be oxidized, two carbons at a time, each reaction using a chain-specific enzyme, before ketogenesis can occur. There are over 20 individual steps in beta-

oxidation some with multiple enzyme complexes. An enzyme block anywhere in this process or a carnitine deficiency will result in hypoketotic hypoglycemia and tissue damage related to the toxic accumulation of unoxidized fatty acids. At least 16 separate enzyme disorders have been identified, many of which may be identified by MS/MS by measuring the accumulation of various acylcarnitines.

Fatty acid oxidation disorders*

- Carnitine transport defect (enzyme unknown) (CUD)
- Carnitine/acylcarnitine translocase (CT) deficiency
- Carnitine palmitoyl transferase I (CPT I) deficiency
- Carnitine palmitoyl transferase II (CPT II) deficiency
- Very long chain acyl-CoA dehydrogenase (VLCAD) deficiency
- Long chain L-3 hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency
- Medium chain acyl-CoA dehydrogenase (MCAD) deficiency
- Short chain acyl-CoA dehydrogenase (SCAD) deficiency
- Multiple acyl-CoA dehydrogenase deficiency (MADD aka Glutaric acidemia II [GA II])
- Trifunctional protein (TFP) deficiency

MCAD is the most common, approximately 1:15,000 births; LCHAD is 1:50,000 and VLCAD, 1:31,000. The other disorders are less common, but NBS has identified infants with all the FAO disorders. All are inherited as autosomal recessive traits. Screening for FAOs is done for all infants in our region.

Clinical features^{32, 33}

FAO disorders have overlapping symptoms and organ involvement. They fall into three major categories as described below.

Hepatic^{34, 35}: There is no typical age of presentation, which may be on the first day of life through adulthood. As of 2010, three infants in our region with MCAD presented with sudden cardio/pulmonary arrest before screening results were known; one infant survived. Precipitating factors are fasting and/or stress associated with intercurrent illness. Patients present with "Reyes-like" symptoms including vomiting, lethargy, hypoketotic hypoglycemia, mild hyperammonemia, hyperuricemia, hypocarnitinemia and abnormal liver function tests. Liver biopsy often shows steatosis. Hepatic presentation is common in MCAD, VLCAD, LCHAD, neonatal CPT I & II and mild CT deficiency. Approximately 25 percent of individuals with MCAD will die during their first episode. In survivors, about 20 percent sustain significant neurological damage, presumably due to hypoglycemia. Patients with LCHAD also develop retinal pigmentary changes and progressive visual loss in childhood in spite of early diagnosis and treatment.

* These are not all the FAO disorders, only the ones thought to be detectable with MS/MS. At this time the sensitivity and specificity of MS/MS to detect all affected infants is unknown.

Cardiac: Cardiac abnormalities include hypertrophic or dilated cardiomyopathy. Pericardial effusion or cardiac failure can lead to death in these patients. FAO disorders with cardiac involvement include carnitine transporter defects, LCHAD, TFP deficiency, neonatal CPT II and VLCAD.

Muscular: There is usually moderate to severe hypotonia with recurrent rhabdomyolysis. Creatinine kinase may be greatly elevated. In infants and children seizures and/or developmental delay may also be present. Rhabdomyolysis is common in the adult form of CPT II, LCHAD, TFP deficiency and VLCAD.

A mother carrying an affected LCHAD fetus is prone to developing a life-threatening acute fatty liver during pregnancy or HELLP syndrome (hemolysis, elevated liver enzymes, low platelets). The reasons for this are not yet understood, but FAO disorders should be considered in infants whose mothers have a history of these pregnancy complications.³⁶

CPT I and Alaska Natives (AN)

The OSPHL and the Alaska State Division of Public Health have identified a high incidence of CPT I in Alaska Native (AN) infants, approximately 1:200 births as opposed to 1:300,000 in non-native populations in our region. The AN infants all have the same mutation (P479L), allowing easy confirmation of suspect NBS

results and testing for siblings. Canadian provinces also report a higher incidence of this condition among their native populations. The incidence of this condition in other Native American populations has not been determined. The majority of these infants have been identified on a routine second screen obtained around 2 weeks of age or even later and the majority have been asymptomatic. Infants and young children with CPT I usually develop symptoms after the newborn period with seizures and/or coma associated with life threatening episodes of fasting hypoglycemia. Treatment consists of avoiding fasting and intravenous glucose support during intercurrent illnesses. Long-term outcome should be favorable if hypoglycemic episodes are minimized or eliminated.

Treatment

Even with screening, some infants with FAO disorders may die before laboratory results are available. Treatment for MCAD and some other FAOs is extraordinarily simple once the diagnosis is suspected. Avoidance of fasting, particularly as infants and young children, is the primary treatment. Carnitine supplementation (100mg/kg/day) is used to provide a pathway for removal of toxic intermediate metabolites in some FAOs. With appropriate treatment hepatic, cardiac and muscular complications can be reduced or eliminated. Patients with these disorders may require IV support

for fluid and calories during intercurrent infections or illnesses. With pre-symptomatic diagnosis and appropriate therapy, outcome can be normal for infants with MCAD.^{36, 37} Outcomes for the other disorders are still being evaluated.

Screening practice considerations

- Neonatal forms of FAO disorders can present in the first few days of life.
- Practitioners must remain alert to the possibility of FAO disorders in any neonate, infant or child with hypoketotic hypoglycemia or “Reyes-like” episodes or mother’s with HELLP syndrome or fatty liver of pregnancy.
- Infants affected with an FAO who are well fed may have normal screening results, masking the presence of the disorder.
- Practitioners caring for Alaska or Canadian Native infants should ensure that infants are tested twice, once between 24–48 hours of age and the second about 2 weeks of age.

Results	Likely causes	Actions
C0 (free carnitine) <7.50 µM/L, or >300 µM/L	<ul style="list-style-type: none"> • Carnitine transport defects possible • Carnitine deficiency • False positive 	NBS nurse faxes results. Medical consultant phones practitioner with follow-up recommendations.
C0/C16 + C18 >100	<ul style="list-style-type: none"> • CPT I possible • False positive 	NBS nurse faxes results. Medical consultant phones practitioner with follow-up recommendations.
C0 (Free carnitine) <7.50 µM/L C4 (Butyryl/Isobutyryl) >1.40 µM/L C5 (Isovaleryl) >0.70 µM/L C6 (Hexanoyl) >0.80 µM/L C14 (Tetradecanoyl) >0.80 µM/L C16 (Palmitoyl) >8.00 µM/L C16:1 (Palmitoleyl) >0.80 µM/L C18 (Octadecanoyl) >3.10 µM/L C18:1 (Oleyl) >4.50 µM/L	<ul style="list-style-type: none"> • CPT II possible • False positive 	NBS nurse faxes results. Medical consultant phones practitioner with follow-up recommendations.
C14 (Tetradecanoyl) >0.80 µM/L C14:1 (Tetradecenoyl) >0.70 µM/L C16 (Palmitoyl) >8.00 µM/L C18 (Octadecanoyl) >3.10 µM/L	<ul style="list-style-type: none"> • VLCAD possible • False positive 	NBS nurse faxes results. Medical consultant phones practitioner with follow-up recommendations.
C16OH (Hydroxy palmitoyl) >0.10 µM/L C18OH (Hydroxy octadecanoic) >0.10 µM/L C18:1OH (Hydroxy oleyl) >0.20 µM/L	<ul style="list-style-type: none"> • LCHAD, TFP possible • False positive 	NBS nurse faxes results. Medical consultant phones practitioner with follow-up recommendations.
C6 (Hexanoyl) >0.80 µM/L C8 (Octanoyl) >0.70 µM/L C10 (Decanoyl) >0.70 µM/L	<ul style="list-style-type: none"> • MCAD possible • False positive 	NBS nurse faxes results. Medical consultant phones practitioner with follow-up recommendations.
C4 (Butyryl/Isobutyryl) >2.10 µM/L	<ul style="list-style-type: none"> • SCAD possible • False positive 	NBS nurse faxes results. Medical consultant phones practitioner with follow-up recommendations.
C4 (Butyryl/Isobutyryl) >2.10 µM/L C5 (Isovaleryl) >0.70 µM/L C5DC (Glutaryl) >0.70 µM/L C6 (Hexanoyl) >0.80 µM/L C8 (Octanoyl) >0.70 µM/L C10 (Decanoyl) >0.70 µM/L C16 (Palmitoyl) >8.00 µM/L	<ul style="list-style-type: none"> • SCAD possible • MADD/GA II possible • False positive 	NBS nurse faxes results. Medical consultant phones practitioner with follow-up recommendations.

The purpose of newborn screening is to identify infants at risk and in need of more definitive testing. As with any laboratory test, both false negative and false positive results are possible. Screening test results are insufficient information on which to base diagnosis or treatment.

Organic Acid Conditions (OA)

OA Condition Essentials

- **Neonatal Emergency:** Infants with severe forms of organic acidemias will be symptomatic within a few days of birth and may die or suffer brain damage if not diagnosed and treated promptly.
- **Incidence:** 1:20,000 births
- **Screening Test:** MS/MS detection of leucine and acylcarnitines. Approximately 15 OAs can be detected through NBS.
- **Confirmatory Tests:** Quantitative amino acids, acylcarnitines, organic acids, enzyme assay and/or mutation analysis
- **Validity:** >99% detected on first screen
- **Treatment:** Specific amino acid dietary restrictions and medications
- **Outcome:** Variable, from poor to excellent, depending on neonatal course, disease severity, compliance with treatment and other environmental factors

Organic acidemias (OA) result from enzyme deficiencies involved in the catabolism of multiple amino acids and other metabolites. Maple syrup urine disease is detected by an elevation of the amino acid leucine and an abnormal leucine/alanine ratio. All the other OAs are detected through elevations in acylcarnitines. All have autosomal recessive inheritance and have a collective incidence of 1:20,000. Screening for OAs is done for all infants in our region.

The following OAs are screened for by MS/MS:

- Beta-ketothiolase deficiency
- Glutaric acidemia, Type I (glutaryl-CoA dehydrogenase deficiency)
- Isobutyryl CoA dehydrogenase deficiency
- Isovaleric acidemia, (isovaleryl-CoA dehydrogenase deficiency)
- Malonic aciduria
- Maple syrup urine disease (branched chain alpha-ketoacid dehydrogenase deficiency)
- Methylmalonic acidemias, methylmalonyl CoA mutase deficiency and defects of B-12 metabolism
- Propionic acidemia
- 3-Hydroxy-3-methylglutaryl (HMG) CoA lyase deficiency
- 2-Methyl-3-hydroxybutyryl CoA dehydrogenase deficiency
- 2-Methylbutyryl CoA dehydrogenase deficiency (mitochondrial acetoacetyl-CoA thiolase deficiency)
- 3-Methylcrotonyl CoA carboxylase (3MCC) deficiency
- 3-Methylglutaconyl CoA hydratase deficiency (3-methyl-glutaconic aciduria, Type I)
- Multiple carboxylase deficiency

Clinical features^{38, 39, 40}

Neonatal onset: Most of these disorders have severe forms that present in the first week of life and constitute a neonatal emergency. Infants are generally well at birth, but develop poor feeding, irritability, lethargy, vomiting, and severe metabolic ketoacidosis, with or without hypoglycemia, in the first few days of life; this progresses to coma and death in the first month if treatment

is not instituted. In methylmalonic and propionic acidemias, ammonia may also be elevated. Isovaleric acidemia is associated with the odor of “sweaty socks.” Maple syrup urine disease has a characteristic “burnt sugar” or “maple syrup” odor which can be noticed in the urine, sweat and ear cerumen of the affected infant as early as the fifth day of life. Isobutyryl CoA dehydrogenase deficiency is associated with a dilated cardiomyopathy. Even with prompt treatment, many infants with neonatal forms of organic acidemias sustain psychomotor damage and may have significant long-term morbidity. These infants may be ill before the results of the screening tests are known. Contact the metabolic consultants urgently if an OA is suspected.

Late onset: Milder variants may present with an acute decompensation brought on by an intercurrent illness similar to those described above, or with failure to thrive, hypotonia, mental retardation or seizures and a history of bouts of vomiting, protein intolerance, acidosis and/or hypoglycemia. While these patients typically have “milder” disease, the neurological damage may be just as severe as those presenting earlier. Newborn screening may be very beneficial to these infants as the initial crisis may be prevented.

Asymptomatic cases: There are numerous reports of cases of isolated 3-methylcrotonyl-CoA carboxylase deficiency who have remained asymptomatic despite biochemical and/or enzymatic confirmation of the condition. The etiology of these variant presentations is not yet understood. Mild forms of methylmalonic acidemia have been found.

Glutaric Acidemia, Type I: Glutaric acidemia, Type I or GA I is an organic acidemia with clinical features unlike those described above.^{40, 41, 42} In this disease, there is an accumulation of glutaric acid and 3-hydroxy glutaric acid, which are believed to be toxic to cells, particularly in the central nervous system. The classic presentation is macrocephaly at or shortly after birth. Infants have a period of apparently normal development but may have soft neurological signs, like jitteriness, irritability and truncal hypotonia. Generally between 6 and 18 months of age, patients will experience an acute encephalopathic episode resulting in damage to the basal ganglia and atrophy of the caudate and putamen. This occurs over the course of a few hours to a day and is irreversible and untreatable. Severe dystonia, dyskinesia and other neurological findings result, either in a static or slowly progressive form. These children are often misdiagnosed as having extra pyramidal cerebral palsy. Approximately 25 percent of GA I patients will present with motor delay, hypotonia, dystonia and dyskinesia that develop gradually during the first few years of life, without any apparent acute crisis. Intellect is relatively intact. Infants with GA I are prone to acute subdural and retinal hemorrhages after minor head trauma. This can be misdiagnosed as child abuse. Finally, 5 percent of all Amish patients have been completely asymptomatic without any crises and normal development. Neurological crises and symptoms rarely occur after five years of age.

Laboratory tests

All these disorders are detected using MS/MS. Leucine can be elevated in infants receiving parenteral nutrition, usually along with other amino acid elevations. In a normal newborn, however, elevations of these compounds are unusual and require rapid follow up. There is evidence that not all affected infants will be found by NBS.⁴²

Treatment

Any infant in whom a neonatal onset organic acidemia is suspected should be treated as a neonatal emergency. Infants with these disorders should in most, if not all, cases be transferred to a major medical center with a metabolic specialist as quickly as possible. The diagnosis, investigations and management are very complicated. Death or permanent neurological deficits can occur rapidly in untreated cases. Infants who are asymptomatic at the time that abnormal screening results are reported may be handled less urgently, depending on the clinical status and individual circumstances. Treatments, which must be continued for life, consist of strict dietary amino acid restrictions and medications.

Infants with GA I, in addition to diet and medications, must have aggressive supportive care during intercurrent illness throughout the first 5–6 years of life. This generally entails hospitalization, IV fluid and calories during all febrile or flu like illnesses.

For individuals with MSUD, isovaleric acidemia and one or two other organic acidemias, prospective and early identification through newborn screening will be life saving and outcomes are expected to be good. 80 percent of infants with GA1, treated pre-symptomatically, have avoided striatal necrosis. For other less common conditions, the outcome is still being evaluated.

Screening practice considerations

- Affected infants must be detected early if major problems are to be prevented.
- Practitioners must remain alert to the possibility of these diseases in any infant with lethargy, acidosis or coma.

The purpose of newborn screening is to identify infants at risk and in need of more definitive testing. As with any laboratory test, both false negative and false positive results are possible. Screening test results are insufficient information on which to base diagnosis or treatment.

Urea Cycle Conditions (UCD)

Urea Cycle Essentials

- **Neonatal Emergency:** Infants with severe hyperammonemia may die in the first week to 10 days if not diagnosed and treated.
- **Incidence:** 1:60,000 births (all 3 disorders)
- **Screening Test:** Citrulline, argininosuccinic acid and arginine by MS/MS
- **Confirmatory Tests:** Quantitative amino acids, urine organic acids and enzyme assay in red blood cells or hepatocytes
- **Validity:** >99% of citrullinemia and ASA on first test. The only arginase deficient infant diagnosed in Oregon was found on the second screen.
- **Treatment:** Neonatal rescue from hyperammonemic coma is complicated and should be done under the guidance of an experienced metabolic physician. Day-to-day hyperammonemia is controlled with a low protein diet, medications and amino acid supplements. Complete or partial liver transplant eliminates the need for diet and may improve development.
- **Outcome:** For those with citrullinemia and ASA who survive a neonatal coma, the outcome is usually fair to poor. Brain damage is common and the risk of hyperammonemia continues throughout life. Complications from arginase deficiency should be preventable with early and continuous treatment.

The urea cycle is the metabolic pathway responsible for the detoxification of ammonia and for the synthesis of arginine and urea. There are six

enzymes in the urea cycle, each of which if missing, will result in hyperammonemia and one of the six disorders of the urea cycle. Each of these enzyme deficiencies has genetic and clinical variability from mild to lethal. Only three UCDs can be detected by newborn screening:

1. Arginase deficiency
2. Argininosuccinic aciduria (ASA)
3. Citrullinemia, Type I & II

Estimated incidence of these conditions is 1:60,000. They are inherited as autosomal recessive traits. Screening for UCD is done for all infants in our region.

Arginase Deficiency⁴³

Clinical features

Arginase deficiency is associated with irritability, inconsolable crying, anorexia, vomiting and developmental delay in infancy. This progresses to spastic tetraplegia with lower limbs more severely affected than the upper, psychomotor retardation, hyperactivity and growth failure. Hyperammonemia may result in encephalopathy, but is often milder than that seen in other urea cycle defects. A severe neonatal form presents with cholestatic jaundice, liver failure and death.

Citrullinemia, Type I (CTLN1) and Argininosuccinic aciduria (ASA)^{44, 45}

Clinical features-Neonatal onset

Infants appear normal at birth and for the first 24 hours. Usually between 24–72 hours symptoms of hyperammonemia will appear as lethargy, vomiting, hypothermia, hyperventilation progressing to coma, cerebral edema and death without intervention. Unfortunately, a misdiagnosis of sepsis is made in 50 percent of the cases, wasting precious time.

In addition to ammonia, both glutamate and glutamine are usually elevated. Specific elevations in citrulline, argininosuccinic acid, arginine and orotic acid are helpful in determining the exact type of urea cycle defect.

Clinical features-Late onset

Late onset forms of urea cycle disorders most often present as non-specific developmental delay, seizures or other neurological symptoms which are associated with a history of repeated bouts of lethargy, vomiting, irritability or headaches. Food refusal and failure to thrive are not uncommon.

Asymptomatic cases

Newborn screening has detected several infants with very mild citrullinemia, who do not require any treatment when healthy, but may be at risk of decompensation under stress, infection or high protein intake.

Citrin Deficiency (Citrullinemia, Type II & Neonatal Intrahepatic Cholestasis [NICCD])⁴⁶

Citrin is a mitochondrial membrane aspartate-glutamate carrier that acts to transfer cytosolic NADH into the mitochondria. There are two distinct disorders associated with citrin deficiency. It is unknown how well NBS tests will identify these patients.

Clinical features-Neonatal onset

Neonatal intrahepatic cholestasis due to citrin deficiency (NICCD) has been found in over 200 Japanese and Asian infants and a handful of non-Asian infants, usually between 1–5 months of age. Liver disease may be accompanied by jaundice and

fatty infiltrates. While liver failure may necessitate transplant in infancy, the liver disease generally resolves by a year of age for most patients. At least one of these infants has progressed to citrullinemia type II at the age of 16 years.

Clinical features-Late onset

Patients with citrullinemia type II (CTLN2) present in childhood or adulthood (11–64 years of age). Symptoms may be acute or develop slowly. These include enuresis, delayed menarche, insomnia, night sweats and terrors, recurrent vomiting, diarrhea, tremors, confusion, lethargy, delusions and episodes of coma. Citrulline and ammonia are elevated. Within a few years of the diagnosis, episodes of pancreatitis, hyperlipidemia and death from cerebral edema generally occur. Hepatocellular carcinoma has been reported in a few cases.

Laboratory tests

Elevations of citrulline and arginine are detected by MS/MS. The laboratory cutoff for citrulline is $\leq 70 \mu\text{M/L}$; for arginine, $\leq 110 \mu\text{M/L}$; argininosuccinic acid, $\leq 1.50 \mu\text{M/L}$. Transient elevations of plasma arginine and citrulline in the newborn are unusual unless the infant is premature and/or receiving parenteral nutrition.

Infants with NICCD may or may not have citrulline elevations. Approximately half of the Japanese patients came to attention with elevated galactose, methionine and/or phenylalanine on NBS prior to the advent of MS/MS. Approximately 10 percent of NICCD patients had normal citrulline.

Treatment (Citrullinemia, Type I & ASA)

All patients with a neonatal presentation represent medical emergencies and outcomes may be variable.

Patients with neonatal onset disease will typically require aggressive treatment with hemodialysis. All patients, both late onset and those rescued from neonatal hyperammonemia, will require treatment with low protein diets and medications to prevent hyperammonemia and remove toxic compounds. The outcome for patients rescued from prolonged neonatal hyperammonemia is dismal. Brain damage is likely. Even patients treated prospectively from birth may not be normal.⁴⁶ Those with late onset disease fare better, and presymptomatic diagnosis and treatment may allow normal development.

Treatment: NICCD and CTLN2

NICCD responds well to protein restriction in infancy for most patients. Those who do not respond or

who develop progressive liver failure graduate to liver transplantation.

Patients with CTLN2 receive a liver transplant, as they will proceed to death without it. Dietary restriction of protein is ineffective. Long-term outcome is unknown.

Screening practice considerations

- Neonatal emergency.
- Infants with neonatal onset disease may be sick or die before screening results are known.
- Practitioners must remain alert to the possibility of these disorders in any newborn with lethargy or coma.
- Arginine may rise slowly in some cases and is more likely to be found on the second screening test.
- Citrin deficiency is more common in Asian infants.

Results	Likely causes	Actions
Arginine $>110 \mu\text{M/L}$	<ul style="list-style-type: none"> • Arginase deficiency possible • Transient argininemia • Liver disease • False positive 	NBS nurse faxes results. Medical consultant phones practitioner with follow-up recommendations.
ASA $>1.50 \mu\text{M/L}$	<ul style="list-style-type: none"> • Argininosuccinic aciduria possible • Liver disease • False positive 	NBS nurse faxes results. Medical consultant phones practitioner with follow-up recommendations.
Citrulline $>70 \mu\text{M/L}$	<ul style="list-style-type: none"> • Citrullinemia, argininosuccinic aciduria possible • Transient citrullinemia • Liver disease • False positive 	NBS nurse faxes results. Medical consultant phones practitioner with follow-up recommendations.
Citrulline $>120 \mu\text{M/L}$ on second specimen	<ul style="list-style-type: none"> • Mild citrullinemia, argininosuccinic aciduria possible • Transient citrullinemia • Liver disease • False positive 	NBS nurse faxes results. Medical consultant phones practitioner with follow-up recommendations.

The purpose of newborn screening is to identify infants at risk and in need of more definitive testing. As with any laboratory test, both false negative and false positive results are possible. Screening test results are insufficient information on which to base diagnosis or treatment.

Other conditions

Galactosemia

Galactosemia Essentials

- **Neonatal Emergency:** 50% will die in the first 7-10 days usually from gram-negative sepsis. Acute liver disease can produce a coagulopathy and vitreous hemorrhage.
- **Incidence:** 1:60,000
- **Screening Test:** GALT test (qualitative enzyme assay); Second tier: Hill test (free galactose and galactose-1-phosphate) is done on every infant with abnormal GALT test.
- **Confirmatory Tests:** Enzyme assay GALT, RBC gal-1-phosphate
- **Validity:** >99% found on 1st specimen, unless transfused
- **Treatment:** Lactose restricted diet
- **Outcome:** Somewhat diminished IQs as a group, verbal and motor dyspraxia in 60%, ovarian failure in 80% of females and post-natal growth delay during childhood

Dietary galactose is most commonly ingested as lactose, the principal carbohydrate of human milk and most non-soy commercial infant formulas; it is hydrolyzed to glucose and galactose in the intestine. After absorption, galactose is metabolized by several enzymes including galactokinase and galactose-1-phosphate uridyl transferase (GALT). When deficient, the latter causes galactosemia (1:60,000 births). Galactosemia is a recessively

inherited condition. Galactosemia screening is done for all infants in our region.

Clinical features⁴⁷

Detection of galactosemia requires urgent follow-up and is considered a neonatal emergency. The early clinical features of severe untreated galactosemia include neonatal hypoglycemia, liver damage, jaundice, weight loss, lethargy and sepsis. Vitreous hemorrhage from coagulopathy has been reported in some infants. Death may result from gram-negative sepsis within 1–2 weeks of birth. If the infant remains untreated and survives the neonatal period, cataracts, cirrhosis, renal Fanconi syndrome and mental retardation are usual.

There are several genetic variants with less severe reduction in the enzyme activity (e.g., the Duarte variant). The screening test is not designed to detect variant galactosemia and is not completely sensitive for this purpose. Most of these cases are asymptomatic and are detected on newborn screening because of abnormalities in GALT and/or Hill Test. The need for treatment of Duarte variant galactosemia is controversial and infant specific. The metabolic consultants are available for consultation.

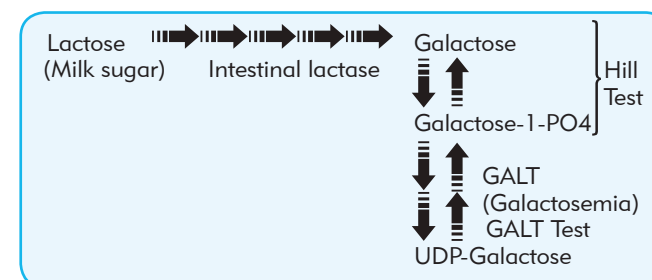
Laboratory tests

Two screening tests are used to detect galactosemia in a two-tiered sequence (see diagram):

1. Galactose (Hill Test): Slight elevations (up to 20 mg/dL) can occur in normal neonates, but galactose metabolites are greatly elevated in infants with galactosemia if they are receiving a lactose-containing formula or breast milk. The Hill test is a fluorometric chemical spot test that

measures galactose and galactose-1-phosphate. Liver disease may also cause an elevation of galactose metabolites. All infants with an abnormal GALT or who have been transfused will be screened with the Hill test.

2. GALT activity (GALT Test): The enzyme test depends upon fluorescence produced by the normal galactose enzyme cascade in red blood cells. A temporarily abnormal result (diminished or absent fluorescence) is found in 1:2,000 infants. The test may be persistently abnormal if the enzyme activity is <50 percent of normal. It does not differentiate milder variants from severe defects. All infants are screened with the GALT test.



Treatment

Galactosemia is treated by dietary galactose restriction. This diet must be followed for life and requires close supervision. Even with early diagnosis and strict dietary restrictions children with galactosemia are at risk for speech disorders, tremors, growth and developmental delays and in females, ovarian failure.

Screening practice considerations

- This disorder kills quickly. Transport all specimens 4–12 hours after collection and no later than 24 hours after collection.
- The GALT test should be abnormal in virtually all severe classic galactosemic infants even if the specimen is obtained before lactose is ingested, unless the infant has been transfused. Obtain a specimen before any transfusion.
- The GALT enzyme is prone to degradation if the sample is delayed in the mail or exposed to excess temperature or humidity. This produces a false positive GALT result.
- Galactose accumulation depends on lactose ingestion so that blood galactose metabolites may be normal in infants being fed a soy-based formula.

Results		Likely causes	Actions
GALT Test	Galactose Metabolites		
<3.5 u/dL	≥20 mg/dL	<ul style="list-style-type: none"> • Severe galactosemia • Variant galactosemia • False positive 	NBS nurse faxes results. Medical consultant phones practitioner with follow-up recommendations.
<3.5 u/dL	<20 mg/dL	<ul style="list-style-type: none"> • Severe galactosemia with little lactose intake • Variant galactosemia • Other enzyme defects in red blood cells • Improperly handled sample (heat damage or transit delay) 	Contact by mail if infant is ≥48 hrs old; contact by fax if <48 hrs old or if not on lactose.

The purpose of newborn screening is to identify infants at risk and in need of more definitive testing. As with any laboratory test, both false negative and false positive results are possible. Screening test results are insufficient information on which to base diagnosis or treatment.

Biotinidase Deficiency

Biotinidase Deficiency Essentials

- **Incidence:** 1:60,000 births
- **Screening Test:** Biotinidase qualitative colorimetric enzyme assay
- **Confirmatory Tests:** Quantitative biotinidase enzyme assay
- **Validity:** 100% found on 1st screen
- **Treatment:** 5-10 mg biotin/day
- **Outcome:** Excellent if compliant with biotin therapy

This recessively inherited disorder affects the cells' ability to recycle the vitamin-cofactor biotin, which impairs the function of mitochondrial carboxylases. The incidence is 1:60,000 births. Screening is done for all infants in the region.

Clinical features^{48, 49}

Infants with profound biotinidase deficiency are normal at birth, but develop one or more of the following symptoms after the first weeks or months of life: hypotonia, ataxia, seizures, developmental delay, alopecia, seborrheic dermatitis, hearing loss and optic nerve atrophy. Metabolic acidosis can result in coma and death.

Infants with partial deficiency (5–10 percent) have been identified through newborn screening and family studies. They may remain asymptomatic with no treatment or exhibit milder symptoms than infants with profound deficiency. A reduced dose of biotin is recommended for these infants as the consequences of possible complications are too great.

Laboratory tests

Detection of enzyme activity is by a qualitative colorimetric assay. In the presence of the enzyme a color change occurs.

Treatment

Daily biotin supplements clear the skin rash and alopecia and improve the neurological status in patients not diagnosed by screening. With early diagnosis and treatment made possible by screening, all symptoms can be prevented.

Screening practice considerations

- The enzyme is prone to damage if the sample is delayed in the mail or exposed to high temperatures or excess humidity.
- Transfusion of red cells prior to drawing the newborn screening specimen will invalidate the biotinidase assay. Obtain a specimen before transfusion.

The purpose of newborn screening is to identify infants at risk and in need of more definitive testing. As with any laboratory test, both false negative and false positive results are possible. Screening test results are insufficient information on which to base diagnosis or treatment.

Results	Likely causes	Actions
Color change does not occur	<ul style="list-style-type: none"> • Biotinidase deficiency possible • False positive 	NBS nurse faxes results. Medical consultant phones practitioner with follow-up recommendations.

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Appendices

Appendix I

Incidence of disorders detected by specific analytes using MS/MS in Oregon
October 28, 2002 - June 30, 2010

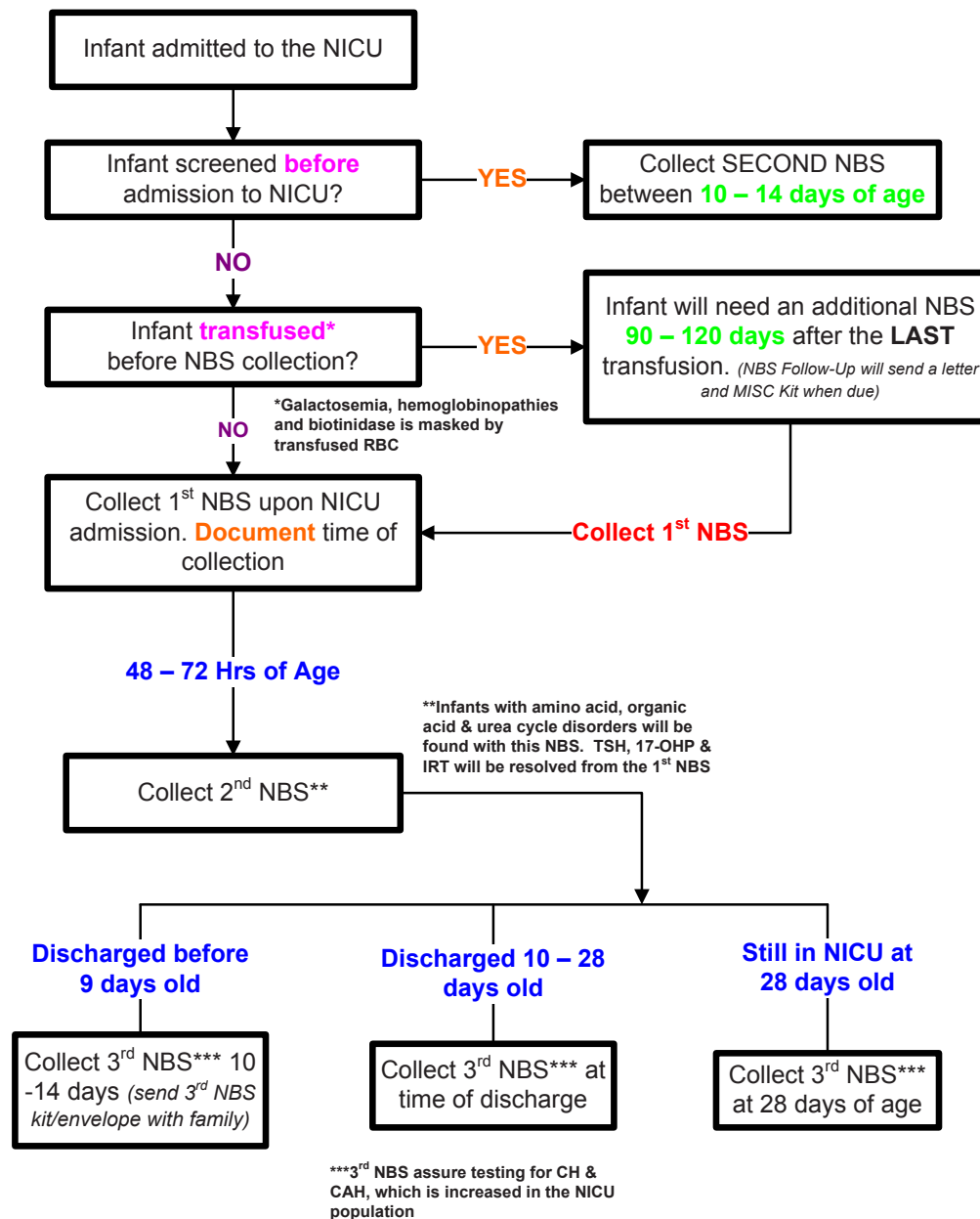
Disorder	Incidence*	Analyte	Analyte ratio
Amino acid disorders	1:9,400		
Arginase deficiency	1:366,000	Arg	
Argininosuccinic aciduria	1:66,000	ASA	
Citrullinemia	1:183,000	Cit	
Homocystinuria	1:366,000	Met	
Hyperphenylalaninemias	1:12,600	Phe	Phe/Tyr
Maple syrup urine disease	-	Leu	Leu/Ala
Tyrosinemias	-	Tyr	
Fatty acid oxidation defects	1:11,100		
Carnitine Uptake Defect	1:122,000	C0↓	
Carnitine/Acylcarnitine carrier defect	-	C0↓ C16↑ C18↑	
Medium chain acyl-CoA dehydrogenase deficiency	1:16,600	C8, C10, C6, C10:1	
Short chain acyl-CoA dehydrogenase deficiency	1:366,000	C4	
Long chain 3-hydroxyacyl-CoA dehydrogenase deficiency	1:183,000	C16OH, C18:1OH, C16:1, C18OH	
Very long chain acyl-CoA dehydrogenase deficiency	1:122,000	C14:1, C16, C14, C16:1 C14:1/ C12:1↑	
Glutaric acidemia GA II	-	C5DC, C6, C8, C10, C14:1, C16:0	
(multiple acyl CoA dehydrogenase deficiency)	-	C4	
CPT I Carnitine palmitoyl transferase deficiency I	1:366,000		C0/(C16+C18)
CPT II Carnitine palmitoyl transferase deficiency II	1:366,000	C18:1, C16↑, C18↑, C0	

Disorder	Incidence*	Analyte	Analyte ratio
Organic acidemias	1:21,500		
Beta-ketothiolase deficiency	-	C5:1, C5OH	
Glutaric acidemias GA I	1:122,000	C5DC	
3-hydroxy-3-methylglutaryl-CoA lyase deficiency (HMG)	-	C6DC, C5OH	
Isobutyryl CoA dehydrogenase deficiency	-	C4	
Isovaleryl CoA dehydrogenase deficiency	1:183,000	C5	
2-methyl-3-hydroxybutyryl CoA dehydrogenase deficiency	-	C5:1, C5OH	
Methylmalonic acidemia	1:73,000	C3	C3/C2
3-methylcrotonyl CoA carboxylase deficiency	1:61,000	C5OH,	
3-methylglutaconic aciduria	-	C5OH	
Multiple carboxylase deficiency	-	C5OH, C3	
Propionyl CoA carboxylase deficiency	1:366,000	C3	C3/C2
Malonic acidemia	-	C3DC	

*Incidence is calculated based on the number of first specimens tested and the number of disorders diagnosed.

Appendix II

Newborn Screening for NICU/SCN Infants



N O R T H W E S T  R E G I O N A L
N E W B O R N S C R E E N I N G P R O G R A M

A collaborative project involving:
Oregon Health Authority
Oregon Health & Science University
Alaska Department of Health and Social Services
Hawai'i Department of Health
Idaho Department of Health and Welfare
Nevada State Health Division
New Mexico Newborn Screening Program

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