

DELAWARE NEWBORN SCREENING PROGRAM

PRACTITIONER'S MANUAL January 2008



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The Newborn Screening Program gratefully acknowledges the contributions of hospitals, nurses, neonatology staffs, laboratory staffs, unit clerks, health information staffs, midwives, physicians, laboratory couriers, and babies and their families for their help in collecting specimens and providing us with accurate information.

INTRODUCTION

Screening of newborns for specified diseases began in the late 1950s and has since become widely accepted throughout the world as an important and effective public health activity. Newborn Screening Programs identify, in the newborn period, certain disorders which, if untreated, result in mental retardation and other disabilities. Early identification allows for early definitive diagnosis and treatment.

The Delaware Newborn Screening Program (NSP) in the Office of Women's and Reproductive Health, Division of Public Health, Department of Health and Social Services, started statewide Phenylketonuria (PKU) screening in 1962. The screening program had expanded by 1979 to include testing for 4 additional disorders: Maple Syrup Urine Disease, (MSUD), Homocystinuria, Congenital Hypothyroidism, and Galactosemia. In 1985, tests for two additional disorders were added: Hemoglobinopathies and Biotinidase Deficiency. In 1999 testing for Homocystinuria, MSUD and Biotinidase was temporarily discontinued.

Since 1999 all Newborn Screening testing has been performed at the State of Delaware Public Health Laboratory. The Laboratory personnel work closely with the Delaware NSP follow-up team and with the hospitals and primary care providers across the state. Results of all screening tests on each baby are provided by electronic data transfer to the NSP follow-up team and by mail to the hospital of birth and to primary care providers.

The State of Delaware Public Health Laboratory uses the most up-to-date technology in screening newborns. The recently added Tandem Mass Spectrometry (abbreviated as MS/MS) along with more traditional technologies allow Delaware to screen for over 30 disorders using only a few spots of blood taken by a heel stick from newborns within the first few days of life.

The disorders screened for are each individually rare, with birth prevalence rates ranging from about 1:4000 to > 1:150,000 infants, so the chance that any single infant will be affected is relatively small. But the costs of not diagnosing one of these conditions, both in terms of human suffering and in financial terms, are substantial. Early diagnosis and treatment for nearly all of the disorders can be expected to result in normal growth and development. Most infants with one of these disorders appear normal at birth. It is only with time that the abnormality may affect the baby's health, growth, and development. A small number of the very rare disorders have no known definite effective treatment and little is known about the ultimate outcome of affected individuals. Rarely, disability may occur in affected children in spite of early diagnosis.

An efficient and effective newborn screening program requires coordinated efforts from a variety of health care providers:

- **PRACTITIONERS:** Prenatal, perinatal and newborn care providers are responsible for the appropriate collecting and handling of screening specimens, for providing families with accurate and current information about the tests and the disorders, and for assuring cooperation in obtaining prompt follow-up in the event of an abnormal result.
- **DELAWARE PUBLIC HEALTH NEWBORN SCREENING LABORATORY:** The laboratory is responsible for performing appropriate tests on submitted specimens, for record keeping, for assuring quality control of laboratory procedures, and for notifying providers and the Delaware Newborn Screening Program Office of results.
- **NEWBORN SCREENING PROGRAM STAFF:** The staff of the Newborn Screening Program is responsible for the identification and tracking of all children identified as having an abnormal or unresolved result, for the administration of an effective and efficient program, for education of practitioners and the public, and for assuring adequate communication among all providers.
- **TREATMENT AND FOLLOW-UP TEAM:** The follow-up team members are responsible for assuring prompt completion of confirmatory tests of infants with abnormal screening results and for assisting practitioners with the management of confirmed cases.

QUALITY ASSURANCE

The Delaware Newborn Screening Program (NSP) is most interested in assuring that its program is of the highest quality.

In 1993 and 2000 Delaware's NSP was reviewed by the National Newborn Screening and Genetics Resource Center (NNSGRC) Technical Assistance Review Team. Delaware received high marks for its program. Several suggestions for improvement were made at each review and the suggestions were promptly adopted.

The NSP has a distinguished Advisory Committee made up of scientists, an attorney, an ethicist, several parents of children with disorders detected by the screening program, and other representatives of public and private organizations interested in newborn screening. The advisory board meets regularly to discuss issues of importance to newborn screening and to assist the NSP in its work.

Information on Medical/Scientific consultants in Delaware and at University Medical Centers in Philadelphia and Baltimore who are available to help evaluate and treat children with the disorders detected by the program is available from the Newborn Screening Program Office. Please call 302-741-2990, or toll free 800-262-3030 for assistance.

The NSP conducts regular quality assurance activities internally and with the various maternity and laboratory services in Delaware hospitals. NSP personnel conduct frequent continuing education sessions with physicians, nurses, and other providers around the state.

NEWBORN SCREENING STAFF

NSP team members are available to provide information on all aspects of the management of children identified by newborn screening. This frequently includes assisting the families and primary care physicians in making prompt and efficient referrals to appropriate pediatric specialists. All of the disorders for which screening is offered require sophisticated diagnosis and treatment best delivered by well-trained experienced specialists working closely with the primary care physician and the family.

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NEWBORN SCREENING IN DELAWARE

Phenylketonuria (PKU), a disorder of the metabolism of the essential amino acid phenylalanine, was the first condition for which cost effective screening was possible. Screening for PKU began in the late 1950's, and by the mid 1960's all states had a PKU screening program. Screening for congenital hypothyroidism was added soon after and subsequently other disorders have been included. The advent of MS/MS in recent years has made effective screening possible for many other disorders. Each state decides which disorders it wishes to screen for. In Delaware, the NSP, assisted by its Advisory Committee and with the approval of the Director of the Division of Public Health, screens for the following disorders:

- Phenylketonuria (PKU)
- Congenital Hypothyroidism
- Galactosemia
- Hemoglobinopathies
- Congenital Adrenal Hyperplasia (CAH)
- Glutaric Aciduria I and other disorders of organic acid metabolism
- Medium Chain Acyl CoA Dehydrogenase (MCAD) Deficiency and other disorders of fatty acid oxidation
- Maple Syrup Urine Disease (MSUD)
- Homocystinuria
- Tyrosinemia and certain other disorders of amino acid metabolism
- Biotinidase Deficiency
- Cystic Fibrosis (CF)
- Carnitine Uptake Deficiency (CUD)

Disorders may be added to or deleted from the list as technology changes and as understanding of the various disorders advances.

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.

It has become customary for many providers to refer to newborn screen as the "PKU test" or "the HMD [hereditary metabolic disease]". Neither is precise and the term "**NEWBORN SCREENING**" is preferred, since many other disorders besides PKU are included in the screening battery and since some of the disorders are not metabolic and some are not hereditary. Babies with other disorders in other states have been mistakenly treated for PKU because any abnormal result was referred to as PKU.

Note: As outlined in State Regulations (Appendix A) newborn screening is a mandatory public health function and the various aspects of the program are exempt from HIPAA Regulations.

TABLE 1**Estimated Frequency Per Live Births of Disorders Screened for by Delaware NSP**

DISORDER	FREQUENCY
Phenylketonuria (PKU)	1:15,000
Congenital Hypothyroidism (CH)	1:4,000
Galactosemia	1:45,000
Hemoglobinopathies	1:400 (African Ancestry)
Congenital Adrenal Hyperplasia (CAH)	1:12,000
Medium Chain Acyl Co-A Dehydrogenase Deficiency (MCAD)	1:15,000
Other Fatty Acid Oxidation(FAO) Disorders	1:40,000
Maple Syrup Urine Disease (MSUD)	1:100,000 (higher in Mennonite)
Homocystinuria	1:70,000
Certain other disorders of amino acid metabolism (NOT including Ornithine Transcarbamylase Deficiency (OTC) 1	1:20,000
Glutaric Aciduria I	1:100,000 (higher in Amish)
Other Organic Acid Disorders	1:20,000
Biotinidase Deficiency	1:60,000
Cystic Fibrosis	1:3000 (varies in different ethnic groups)
Carnitine Uptake Deficiency (CUD)	1:40,000

TABLE 2

Summary of Disorders Screened for by Delaware NSP

DISORDER	ANALYTE MEASURED	RESULTS IF UNTREATED	TREATMENT
Phenylketonuria (PKU)	Phenylalanine level (Phe)	Mental retardation, seizures	Low phe diet
Congenital Hypothyroidism (CH)	Thyroid stimulating hormone (TSH)	Mental retardation, growth delay	Thyroid hormone
Galactosemia	Total galactose, galactosemia enzyme (GALT)	Infection, cataracts, liver disease, mental retardation, etc.	Galactose free diet
Congenital Adrenal Hyperplasia (CAH)	17- α Hydroxy progesterone (17-OHP)	Electrolyte imbalance, shock, infant death	Adrenal hormone replacement
Hemoglobinopathies (most important, Sickle Cell Disease)	Hemoglobin isoelectric focusing	Multiple medical complications	Antibiotic prophylaxis, specialized preventive health care
Medium Chain Acyl-CoA Dehydrogenase (MCAD) Deficiency	Levels of fatty acid acylcarnitines - C8, C6, C10:1	Variable, but may include sudden death, seizures, neurologic syndromes	Diet, avoiding fasts, certain medications
Other Fatty Acid Oxidation (FAO) disorders	Levels and ratios of various fatty acid acylcarnitines	Variable, but may include sudden death, seizures, neurologic syndromes	Diet, avoiding fasts, certain medications
Maple Syrup Urine Disease (MSUD)	Blood levels of leucine/isoleucine	Neonatal coma, seizures, acidosis, mental retardation	Diet low in branched chain amino acids
Glutaric Aciduria I	Glutaryl carnitine, C5-DC	Seizures, athetosis, motor disability	Diet, certain medications
Other Organic Acid disorders	Specific acylcarnitines	Variable	Variable
Homocystinuria	Methionine level	Characteristic body habitus, eye anomalies, mental retardation, hypercoagulable	Diet, medications
Other disorders of amino acid metabolism	Blood arginine, tyrosine, citrulline	Variable	Diet, variable
Biotinidase Deficiency	Biotinidase activity	Seizures, rash, mental retardation, hearing loss	High dose biotin
Cystic Fibrosis	Immunoreactive Trypsinogen (IRT)	Progressive lung disease, malabsorption, malnutrition	Complex respiratory and gastrointestinal support
Carnitine Uptake Deficiency	Carnitine	Hypoglycemia, cardiomyopathy seizures, delay	Carnitine

CONGENITAL HYPOTHYROIDISM

Congenital hypothyroidism is the lack of adequate amounts of functional thyroid hormone in the newborn period. Thyroid hormone (T4) is important in many metabolic functions and is essential for normal growth and development. Infants with congenital hypothyroidism have an elevated thyroid stimulating hormone (TSH). The birth prevalence rate of congenital hypothyroidism is about 1:4,000.

Clinical Features

A child with untreated congenital hypothyroidism will have delayed growth and will develop moderate to severe mental retardation, and a complex of characteristic features (cretinism). Affected infants with untreated congenital hypothyroidism may appear relatively normal for several months of age though serious irreversible central nervous system damage may be occurring. In the absence of a universal screening program diagnosis of congenital hypothyroidism before age 2-3 months is rare.

Clinical symptoms or signs of untreated congenital hypothyroidism may include prolonged neonatal jaundice, constipation, lethargy, poor muscle tone, feeding problems, a large tongue, puffy face, large fontanel, distended abdomen, umbilical hernia, and hypothermia.

Causes of Congenital Hypothyroidism

The most common causes are total or partial failure of development of the thyroid gland or its development in an abnormal location (an ectopic gland). Less commonly, congenital hypothyroidism results from damage to fetal thyroid by medications (antithyroid drugs or excess iodine) used by the mother during pregnancy, or results from primary failure of the hypothalamic - pituitary axis with the hypothalamus failing to produce adequate amounts of thyroid stimulating hormone (TSH). In some cases congenital hypothyroidism results from a genetic defect in thyroid hormone synthesis.

Laboratory Tests

Thyroxine stimulating hormone (TSH) is measured. Thyroxine (T4) is measured in children with elevated TSH.

TABLE 3

Normal Values and Laboratory Criteria for Requesting Repeat Samples

ANALYTE	NORMAL	PHONE FOLLOW-UP	MAIL FOLLOW-UP
TSH	< 20 μ IU/mL	> 75 μ IU/mL	20 - 75 μ IU/mL

All phoned results are followed by mailed confirmation. All tests are screening tests. Abnormal results need full evaluation before a diagnosis is confirmed. Cut-off values are evaluated periodically and subject to change.

Confirmatory Testing and Management

When the screening results are abnormal, a blood sample for T4, free T4 and TSH measurement should be collected by venipuncture as soon as possible (certainly within 24 hours) to confirm abnormal screening results. In cases in which TSH is unequivocally elevated, and T4 is low, treatment can be started as soon as the serum is obtained, pending final confirmation. When possible a thyroid scan or thyroid ultrasound are recommended, but treatment should not be delayed beyond 24 hours awaiting imaging.

Treatment of congenital hypothyroidism is relatively simple and effective in most children. Thyroxine is administered daily. Because some children present certain complex issues, evaluation and treatment are best handled in consultation with a Pediatric Endocrinologist. As part of comprehensive care, children should also have periodic developmental testing. If treatment is started early and maintained, development can be expected to be normal.

Screening Practice Considerations

Detection of hypothyroidism does NOT depend on protein or lactose ingestion. Greater than 90% percent of hypothyroid infants are detected on the first specimen even if it is collected a few hours after birth. For these reasons, it is important to obtain a screening specimen on every infant prior to discharge from the hospital or birth center. In about 10% of cases hypothyroidism is only detected after the first week of age, that is on the second screen. Practitioners must remain alert to clinical symptoms in older infants despite normal initial screening. If a practitioner clinically suspects hypothyroidism, he/she should arrange for testing no matter what the results of the newborn screen.

Thyroid Function in Pre-term Infants

In pre-term, low birth weight infants, T4 levels are lower than in term infants. This does not appear to be due only to low Thyroid Binding Globulin (TBG) and TSH levels are not elevated even in the presence of low T4. Pre-term infants with a low T4 result need special observation to ensure that the low T4 levels rise into the normal range as the infant matures (which may take several weeks). Previously Delaware's primary screening for congenital hypothyroidism was measurement of T4 with TSH measurement in selected cases. At this time TSH is the primary metabolite measured so the well-described low T4 of extreme premature babies will no longer be observed.

False positive TSH results may occur when the specimen is collected within the first few hours after birth, when TSH transiently and apparently physiologically rises.

Rarely TSH may be elevated due to cross reactivity with certain antibodies transmitted from the mother. Prompt serum testing clarifies this effectively.

The rare primary disorders of hypothalamic or pituitary function are associated with Low T4 but with normal or low TSH. These disorders will not be detected in states (including Delaware) that measure TSH as the primary metabolite.

PHENYLKETONURIA (PKU)

Phenylketonuria (PKU) is an autosomal recessive disorder of the metabolism of the amino acid phenylalanine. The birth prevalence rate is about 1:15,000. In the classic form the enzyme, phenylalanine hydroxylase (PAH) which catalyzes the conversion of phenylalanine to tyrosine, is absent or altered so phenylalanine accumulates. Elevated phenylalanine is toxic to the developing nervous system.

Clinical Features in Children with untreated PKU

Infants with untreated PKU may appear to be normal for many months. However, without treatment, phenylalanine accumulates in the central nervous system resulting in mental retardation, microcephaly, seizures, hyperactivity, movement disorder and eczema. In older untreated patients the skin and hair are usually fair, the eyes blue and there may be a “mousey odor” of the skin or urine.

Plasma phenylalanine is usually not detectably elevated in cord blood of affected infants. In affected children phenylalanine begins rising immediately after birth and rises rapidly over 12-48 hours. Phenylalanine blood level is usually elevated in affected infants within 24 hours and uniformly elevated by 48 hours after birth if the infant has received adequate dietary protein.

Laboratory Tests

Hyperphenylalaninemia is detected by MS/MS analysis of the blood spot. Phenylalanine:tyrosine ratio is also calculated.

TABLE 4

Normal Values and Laboratory Criteria for Requesting Repeat Samples

ANALYTE	NORMAL	PHONE FOLLOW-UP	MAIL FOLLOW-UP
<i>Phenylalanine (MS/MS)</i>	<i>Phe < 92.8 μmole/L</i>	<i>Phe ≥ 115.0 μmole/L</i>	<i>Phe ≥ 92.8 μmole/L and < 115.0 μmole/L</i>

All phoned results are followed by mailed confirmation. All tests are screening tests. Abnormal results need full evaluation before a diagnosis is confirmed. Cut-off values are evaluated periodically and subject to change.

Treatment

With proper treatment of PKU, mental retardation is preventable. The outcome in children identified and treated within the first two weeks is excellent compared to children treated later. However, studies have shown some increase in relatively mild learning problems even in some children treated optimally. Treatment should be started as soon after birth as possible in any infant with phenylalanine levels over **115 μ mole/L** and should be continued indefinitely. Frequent monitoring is required, especially in the first weeks. Variant, often benign, forms of hyperphenylalaninemia initially may be indistinguishable from true PKU by screening alone.

If treatment of affected children is not started until several weeks of age, the outcome is poorer and the ultimate developmental achievement will likely be lower. Affected children who are not treated until after six months may show some improvement in development with treatment, although they are likely to remain substantially delayed. Older untreated patients usually show little change in functional level with treatment, but a low phenylalanine diet may help to control behavior problems. (Refer to Appendix E, Specialty Formula Fund Policy.)

Screening Practice Considerations

It has been frequently stated that at least 24 hours of normal feeding on the breast or with formula is required to detect all PKU infants. Determination of phenylalanine levels by MS/MS technology is believed to improve detection even in very young infants. In any case at least 75% of affected infants will be detected even if testing is done without the full 24 hours of feeding. Children with variant forms of hyperphenylalaninemia may only be detectable after several days of protein intake.

If an infant is tested "early" (before 24 hours of milk feedings) a repeat test must be done **within 72 hours - 14 days of age** since treatment delayed due to delay in diagnosis is associated with poorer outcome. (Refer to Table 19, page 41.)

Contamination of the filter paper with food or liquids containing NutraSweet (Aspartame) may cause false positive results.

Variant forms of PKU (Hyperphenylalaninemia)

There are several variant forms of hyperphenylalaninemia in which the plasma phenylalanine levels are elevated over "normal", but are lower than found in PKU. In infancy, it may be difficult to distinguish children with variants from those with PKU. Some children with a variant form may be at risk for mental retardation, but for others the risk is negligible. These are complicated issues and specialized consultation is needed to distinguish among the various forms. In some children unnecessary dietary treatment could be harmful.

Some recently identified forms of hyperphenylalaninemia are caused by defects of bipterin metabolism. In children with these rare defects, blood phenylalanine levels are variable. These patients may have progressive neurological damage with seizures and steady deterioration which can become 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 disorders, **ALL** infants with persistently abnormal levels of phenylalanine should be tested by special blood and urine tests for bipterin abnormalities.

Maternal PKU and Hyperphenylalaninemia

Pregnant women with poorly controlled PKU who have elevated blood phenylalanine have an increased risk of miscarriage, and their offspring (who usually do not have PKU) often have intra uterine growth retardation. Many of these infants have microcephaly, mental retardation, and/or congenital heart defects. These infants have a transient elevation of phenylalanine at birth ($228-500 \mu\text{mole/L}$) which falls to normal promptly. Measurement of blood phenylalanine on the **mothers** of infants with transient hyperphenylalaninemia is recommended, particularly if the infant's sample was collected in the first 24 hours after birth. In women with PKU, if blood phenylalanine can be kept low by a carefully monitored phenylalanine restricted diet prior to conception and during pregnancy, damage to the fetus can be avoided.

CONGENITAL ADRENAL HYPERPLASIA (CAH)

Congenital Adrenal Hyperplasia (CAH) is the term used to describe a number of autosomal recessively inherited disorders of production of essential adrenal hormones. The most common (90%) of these disorders is 21-hydroxylase deficiency. 21-hydroxylase is one of the enzymes important in the synthesis of the adrenal hormones, cortisol and aldosterone. 21-hydroxylase deficiency in its severe form (“salt wasting”) occurs in about 1:12,000 live births.

Clinical Features

In female infants the salt wasting form of 21-hydroxylase deficiency most frequently presents in the immediate newborn period as ambiguous genitalia. In males it generally presents within the first 3 weeks of life as hypoglycemia, hypotension, hyponatremia and hyperkalemia. (Though rarely it may present later). Affected babies at 5-7 days and older may present critically ill in shock and the condition may be life threatening. Treatment involves emergency care for the shock and then life long replacement of the missing hormones.

Females are virilized because the absence of cortisol and aldosterone results in the loss of feedback inhibition of ACTH producing excess androgenic hormones and virilization. Occasionally a female is so extensively virilized that she appears to be male and is not identified as being affected until later, normally 5-21 days as is typical of males. Both males and females may have areas of increased pigmentation.

Cause of Congenital Adrenal Hyperplasia

All forms of CAH are autosomal recessive. Each is a deficiency of one of the enzymes involved in production of cortisol and aldosterone from cholesterol.

Laboratory Tests

The screening is for the 21 hydroxylase form only and involves measurement of 17 hydroxyprogesterone (17 OHP). This steroid is elevated in children with 21-hydroxylase deficiency. Levels of 17 OHP are normally high in the first hours of life and high in low birth weight infants. This may make interpretation of screening results difficult in the first 12 hours of life and in low birth weight babies.

Confirmatory Testing and Management

When a “critical” elevation is detected, the baby should be seen immediately and confirmation sought. Confirmation is obtained by measurement in serum of a number of steroid hormones. Serum glucose and electrolytes also need to be measured promptly. Since CAH is complex, evaluation and treatment are best handled in consultation with a pediatric endocrinologist. Other consultants such as a pediatric urologist and geneticist may be required as well.

When the diagnosis of salt wasting 21-hydroxylase deficiency is confirmed, hormone replacement is begun immediately, usually with glucocorticoids and mineralocorticoids. The choice of hormone, the dose, and timing of treatment must be individualized for each affected child.

There are at least two variant forms of 21-hydroxylase deficiency. One is known as “non-salt wasting” or “simple virilizing.” This is apparently associated with partial deficiency of the enzyme and is less likely to present as severe electrolyte abnormality but may be associated with virilization of female genitalia, precocious puberty and abnormalities of sperm production in the male. Treatment is generally with glucocorticoids. The other variant is known as “non-classical” and is associated with mild deficiency of the enzyme. It is usually not clinically important in early childhood but may cause rapid growth and early virilization as well as abnormal menses and reduced fertility in females. Children with simple virilizing and non-classical may be detected on newborn screening. Great care is required in determining the appropriate medical and psychological management of children with the simple virilizing and non-classical forms.

Screening Practice Consideration

Detection does **NOT** depend on lactose or protein ingestion. Low birth weight and critically ill babies often have higher levels of 17 OHP and, therefore, great care is required in interpretation of screening results in those babies.

TABLE 5

Normal Values and Laboratory Criteria for Requesting Repeat Samples

ANALYTE	BIRTH WEIGHT	NORMAL	PHONE FOLLOW-UP	MAIL FOLLOW-UP
<i>17-OHP</i>	<i>< 1300 gm</i>	<i>< 95 ng/mL</i>	<i>≥ = 120 ng/mL</i>	<i>95-120 ng/mL</i>
<i>17-OHP</i>	<i>1300-2199 gm</i>	<i>< 60 ng/mL</i>	<i>≥ = 85 ng/mL</i>	<i>60-85 ng/mL</i>
<i>17-OHP</i>	<i>≥ 2200 gm</i>	<i>< 35 ng/mL</i>	<i>≥ = 45 ng/mL</i>	<i>30-45 ng/mL</i>

All phoned results are followed by mailed confirmation. All tests are screening tests. Abnormal results need full evaluation before a diagnosis is confirmed. Cut-off values are evaluated periodically and subject to change.

SICKLE CELL ANEMIA AND OTHER HEMOGLOBINOPATHIES

Neonatal diagnosis, parental education, and early appropriate treatment of sickle cell anemia (SS disease) and other clinically significant hemoglobinopathies have significantly lowered morbidity and mortality among affected infants.

Homozygous/sickle cell anemia (SS disease) occurs when a copy of the altered form (mutation) of the gene for the beta globin chain of hemoglobin (the “S” mutation) is inherited from each parent. Clinically significant sickling syndromes also occur when an S mutation is inherited along with certain other mutations in the beta chain (e.g. a C mutation resulting in an S/C phenotype) or with certain thalassemia mutations. These mixed heterozygous conditions, including the relatively common hemoglobin SC disease, as a group, tend to be clinically less severe than homozygous sickle cell anemia, though severe medical complications may occur in some individuals. The birth prevalence rate of clinically significant sickling disorder syndromes in the African American population is about 1:400, and is about 1:15,000 for the general population.

Clinical Features

Sickle cell syndromes are variable in their clinical manifestations and may involve multiple organ systems. The early manifestations, which may be life threatening, include fever and susceptibility to overwhelming infection, splenic sequestration, severe anemia and aplastic crisis. Other complications of sickle cell syndromes include osteomyelitis, vaso-occlusive pain syndromes, acute chest syndrome, cerebrovascular accident (stroke), priapism, pyelonephritis, retinopathy and others. Mortality rates which have been reported to be as high as 25% in the first 3 years of life prior to initiation of newborn screening programs have fallen to less than 10%.

Other significant hemoglobinopathies, including hemoglobin C disease and various thalassemias, are also variable in their clinical presentations. Their manifestations range from very mild chronic anemia to clinical states of severe dyserythropoiesis requiring a lifetime of transfusion support. Pediatric hematologic consultation is strongly suggested for children with hemoglobinopathies.

Laboratory Tests

The initial screening test involves an estimation of the relative concentration of the various hemoglobins via thin layer isoelectric focusing. This test is sensitive and specific, even in the newborn period. It is performed using a small amount of hemoglobin obtained from the dried blood spot from the newborn screening filter paper.

TABLE 6

Normal Values and Laboratory Criteria for Requesting Repeat Samples

ANALYTE	NORMAL	PHONE FOLLOW-UP	MAIL FOLLOW-UP
<i>Hemoglobin Isoelectric Focusing</i>	<i>Hgb FA</i>	<i>Probable Disease FS, FSC, FC, FS>A, F only</i>	<i>Probable Heterozygotes FAS, FAC, FAE, FAX, FA Bart's (FAB), etc.</i>

All phoned results are followed by mailed confirmation. All tests are screening tests. Abnormal results need full evaluation before a diagnosis is confirmed.

Different combinations and hemoglobin patterns are possible; refer to Table 7, page 18, Hemoglobinopathies.

TABLE 7
HEMOGLOBINOPATHIES

RESULTS	LIKELY CAUSE	ACTION
<i>FS (absence of A)</i>	<ul style="list-style-type: none"> • <i>Sickle Cell Anemia OR</i> • <i>Sickle Beta Thalassemia</i> 	<i>Contact practitioner by phone with recommendations for diagnosis and treatment</i>
<i>FSC (absence of A)</i>	<ul style="list-style-type: none"> • <i>Sickle Hemoglobin C Disease (Hb SC disease)</i> 	<i>Contact practitioner by phone with recommendations for diagnosis and treatment</i>
<i>FC (absence of A)</i>	<ul style="list-style-type: none"> • <i>Hemoglobin C Disease</i> 	<i>Contact practitioner by phone with recommendations for diagnosis and treatment</i>
<i>FE (absence of A)</i>	<ul style="list-style-type: none"> • <i>Homozygous Hemoglobin E</i> • <i>Hemoglobin E-Beta Thalassemia</i> 	<i>Contact practitioner by phone with recommendations for diagnosis and treatment</i>
<i>FSA</i>	<ul style="list-style-type: none"> • <i>S Beta Thalassemia</i> • <i>Sickle cell anemia following transfusion</i> 	<i>Contact practitioner by phone with recommendations for diagnosis and treatment</i>
<i>FAS</i>	<ul style="list-style-type: none"> • <i>Hemoglobin S Trait</i> • <i>Sickle cell anemia following transfusion</i> 	<i>Report by letter regarding retesting and significance</i>
<i>FAC</i>	<ul style="list-style-type: none"> • <i>Hemoglobin C Trait</i> • <i>Hemoglobin C disease following transfusion</i> 	<i>Report by letter regarding retesting and significance</i>
<i>FA & slow band ("X")</i>	<ul style="list-style-type: none"> • <i>Most commonly hemoglobin E, O, D, or G trait</i> 	<i>Report by letter regarding retesting and significance</i>
<i>FA & fast band (Bart's)</i>	<ul style="list-style-type: none"> • <i>Bart's hemoglobin is a marker for an alpha thalassemia condition</i> 	<i>Report by letter regarding retesting and significance</i>
<i>F only</i>	<ul style="list-style-type: none"> • <i>Pre-term infant or</i> • <i>Beta Thalassemia</i> 	<i>Contact practitioner by phone with recommendations regarding retesting and significance</i>
<i>F light A</i>	<ul style="list-style-type: none"> • <i>Pre-term infant or</i> • <i>Beta Thalassemia</i> 	<i>Contact practitioner by phone with recommendations regarding retesting and significance</i>
<i>Predominance of A AF</i>	<ul style="list-style-type: none"> • <i>Transfused infant</i> • <i>Patient outside of neonatal age range</i> 	<i>Report by letter regarding retesting and significance</i>

Confirmatory Testing

Newborn screening tests are not diagnostic and **MUST** be confirmed on a whole blood specimen. Solubility testing (Sickle-dex) is never an appropriate test to use alone in diagnosing hemoglobinopathies.

Treatment

Early education of families about the disorders, use of prophylactic antibiotics, provision of emergency care for fever and infections, and assurance of appropriate immunizations including pneumococcal vaccine have resulted in a dramatic decline in early mortality from sickle cell anemia. Various other treatments, including the judicious use of blood products are useful in some affected children. Continuing family education, specialized genetic counseling, and support groups have proven to be effective.

Carrier Detection Makes Hemoglobin Screening Different

The screening assay for hemoglobin will identify carriers (Heterozygotes or children with so called sickle trait) as well as those affected with disease. Many more children will be identified with trait than with disease not only for sickle cell syndromes, but also for other variant hemoglobins. Several principles are clear and important when handling this genetic information: The family is entitled to the information and it is private. The Delaware Newborn Screening Program will inform the primary care practitioner and the family of all results. The primary care practitioner is obliged to assist in informing and counseling the family. The parents are at increased risk, (at least 1/40 compared to 1/400 for Hgb S); of having a subsequent child affected with a hemoglobin disorder because at least one of the parents is now known (indirectly) to be a heterozygote. The family should be offered testing and genetic counseling. If the family declines participation, this should be documented. **The newborn screening blood sampling is only a screen and is NOT a definitive diagnostic procedure.**

Screening Practice Considerations

Newborn screening for hemoglobinopathies is performed only on the **FIRST SPECIMEN**, unless an abnormality is detected. Reliable screening does not require a protein feeding and is not affected by lactose feeding.

Some hemoglobinopathies, particularly the beta thalassemys, are not reliably detected through newborn screening and a normal screening test does not eliminate the possibility that a patient might have a hemoglobinopathy. Further testing or consultation should be sought if there is clinical suspicion.

Infant Transfusion

Transfusion of red blood cells prior to drawing the newborn screening specimen will invalidate the hemoglobinopathy test. Hemoglobin patterns of affected infants may be masked by donor cells if the infant is transfused. It is recommended that the practitioner obtain the screening specimen **BEFORE TRANSFUSION** whenever possible to assure early diagnosis of disease states. If the infant is transfused prior to obtaining the two required specimens, a repeat specimen will be requested 90 days after the last transfusion.

BIOTINIDASE DEFICIENCY

Biotinidase deficiency is an autosomal recessive disorder in the regeneration of biotin. Biotinidase deficiency results in the impairment of the metabolism of various enzymes particularly mitochondrial carboxylases. The birth prevalence rate is estimated to be 1:60,000 births.

Clinical Features

Infants with biotinidase deficiency appear 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, atypical seborrheic dermatitis, hearing loss, and optic nerve atrophy. Some affected children may have episodes of life threatening metabolic acidosis.

Laboratory Tests

Determination of enzyme activity is by a quantitative measurement of enzyme level.

TABLE 8

Normal Values and Laboratory Criteria for Requesting Repeat Samples

ANALYTE	NORMAL	PHONE FOLLOW-UP	MAIL FOLLOW-UP
<i>Biotinidase</i>	<i>Activity present > 21.0 ERU</i>	<i>Activity absent <I = 7.0 ERU</i>	<i>Partial activity 7.0 - 21.0 ERU</i>

All phoned results are followed by mailed confirmation. All tests are screening tests. Abnormal results need full evaluation before a diagnosis is confirmed. Cut-off values are evaluated periodically and subject to change.

Confirmatory Testing

Newborn screening tests are not diagnostic and **MUST** be confirmed on a whole blood specimen. Confirmatory testing may be arranged through the Newborn Screening Program Medical Genetics Consultant.

Treatment

Daily biotin supplements clear the skin rash and alopecia and improve the neurological status in children diagnosed outside the newborn period, that is in children not identified by newborn screening. With early diagnosis and treatment, symptoms can be prevented.

Screening Practice Considerations

Detection of the deficiency does not depend on protein or lactose ingestion and, therefore, it can be identified on a specimen taken before protein feeds (i.e. an early specimen). If however, the infant has been recently transfused the test is less sensitive and should be repeated at the earliest, several days after the last transfusion. It is preferable to obtain the initial specimen **BEFORE TRANSFUSION**. Care is required in obtaining and handling the specimen since the enzyme is prone to damage if the sample is delayed in transport to the lab or exposed to high temperatures.

GALACTOSEMIA

Galactosemia is an elevation of galactose in the blood. Lactose, the principle carbohydrate of human milk, cow's milk, and most non-soy formulas, is a disaccharide made up of the monosaccharides glucose and galactose. Lactose is hydrolyzed to glucose and galactose in the intestine. In the liver galactose is converted to glucose-1-phosphate by a series of biochemical reactions. Classic galactosemia and related conditions are autosomal recessive traits. Classic galactosemia occurs in 1:60,000 births. The classic form of galactosemia is due to almost total deficiency of galactose-1-phosphate uridyl transferase (known as GALT or the tranferase), the enzyme which catalyzes the conversion of galactose-1-phosphate to glucose-1-phosphate. The enzyme deficiency results in elevation of galactose-1-phosphate and certain of its metabolic products in blood and other tissues.

Clinical Features

The clinical features include neonatal hypoglycemia, liver dysfunction, prolonged neonatal jaundice, failure to thrive, lethargy, and susceptibility to overwhelming infection particularly due to *E. coli* and other gram negative bacteria. Later manifestations include cataracts, chronic liver disease, renal dysfunction, failure to thrive, premature ovarian failure, and mental retardation.

There are several genetic variants associated with lesser reductions in the activity of the enzyme (e.g. Duarte Variant). Many of the variants are asymptomatic and of little or no clinical importance. However, they are often associated with elevated blood galactose which will be detected on newborn screening and will need to be carefully distinguished from the clinically important variants. Infants suspected of having any of the forms of galactosemia need prompt specific diagnosis.

Laboratory Tests

1. Measurement of the red blood cell level of Galactose-1-phosphate uridyl transferase (GALT) in dried blood spot samples using a colorimetric method.
2. Measurement of red blood cell total galactose concentrations in dried blood spot samples using an enzymatic colorimetric method.

TABLE 9

Normal Values and Laboratory Criteria for Requesting Repeat Samples

ANALYTE	NORMAL	PHONE FOLLOW-UP	MAIL FOLLOW-UP
<i>GALACTOSE</i>	<i>< 12 mg/dL</i>	<i>>/= 18.0 mg/dL</i>	<i>Total Galactose 12 to 17.99 with GALT > 2.3 U/gm Hb</i>
<i>Gal-1-phosphate uridyl transferase (GALT)</i>	<i>> 2.3 U/gm Hb</i>	<i>GALT < 1.4 U/gm Hb or GALT 1.4 - 2.3 U/gm Hb & baby on lactose free diet or GALT 1.4 - 2.3 U/gm with Total Galactose \geq 12 mg/dL</i>	<i>GALT 1.4 - 2.3 U/gm with Galactose < 12 mg/dL and baby on lactose diet</i>

All phoned results are followed by mailed confirmation. All tests are screening tests. Abnormal results need full evaluation before a diagnosis is confirmed. Cut-off values are evaluated periodically and subject to change.

Confirmatory Testing

Newborn screening tests are not diagnostic and suspected galactosemia **MUST** be specifically confirmed on a liquid blood specimen sent to an appropriate reference laboratory (available in Philadelphia, Pennsylvania; Baltimore, Maryland; or elsewhere).

Treatment

Most complications of galactosemia syndromes are effectively treated by a dietary exclusion of all galactose. This diet must be followed for life and requires close supervision. The long-term developmental outlook for children identified and treated early is good compared to the development expected in untreated children. However, even with early diagnosis and strict dietary restrictions children with galactosemia are at risk for speech and language disorders, relatively mild developmental delay and in females, ovarian failure. Affected children should be followed regularly by appropriate specialists.

Screening Practice Considerations

GALT measurement is abnormal in all infants with severe (classical) galactosemia even if the specimen is obtained before lactose and protein are ingested, unless the infant has had a recent transfusion. It is preferable to obtain the initial specimen **BEFORE TRANSFUSION** since GALT and galactose are measured in red blood cells.

Galactose accumulation depends on lactose ingestion so that blood galactose is not elevated in affected infants receiving lactose free formula such as most soy-based formulas.

The enzyme is prone to damage if the sample is delayed in the mail or exposed to high temperatures; so false positive GALT measurements are not uncommon.

Galactokinase Deficiency

Galactokinase is an enzyme which catalyzes the phosphorylation of galactose to galactose-1-phosphate. The absence of this enzyme in untreated children is associated with the development of cataracts in infancy and possibly with some degree of mental retardation. The life-threatening complications of severe galactosemia do not occur.

Epimerase Deficiency

Epimerase deficiency is a rare, usually benign, disorder characterized by the absence of the enzyme, epimerase, in red cells. RBC epimerase deficiency results in elevated RBC galactose and will be detected on newborn screening.

Specific testing is needed to distinguish among the various disorders of galactose metabolism.

CYSTIC FIBROSIS (CF)

Cystic Fibrosis (CF) is an autosomal recessive disorder caused by an altered protein - the cystic fibrosis trans membrane regulator. The altered protein results in altered movement of chloride across membranes in various organs - particularly in the lungs and the pancreas. The birth prevalence rate of CF is about 1:2,500 of children of Northern European ancestry.

Clinical Features

Children with CF usually present in the first two years of life with recurrent/persistent lower respiratory tract disease and poor weight gain associated with malabsorption. Children with this presentation are chronically ill with limited life expectancy. There are many other features and variable presentations. Children may present with nasal polyps, rectal prolapse, with respiratory disease and no signs of malabsorption or with diarrhea and malabsorption but minimal respiratory signs and symptoms. Other, less common, presentations of CF include meconium ileus in the newborn, recurrent pancreatitis in older children and young adults, and infertility in males due to bilateral congenital absence of the vas deferens.

Laboratory Tests

Immunoreactive trypsinogen (IRT) is measured in the blood spot.

TABLE 10

Normal Values and Laboratory Criteria for Requesting Repeat Samples

ANALYTE	NORMAL	PHONE FOLLOW-UP	MAIL FOLLOW-UP
IRT	< 70 ng/mL	>/= 100 ng/mL	70 -100 ng/mL
IRT	< 70 ng/mL	> 70 ng/mL IF first screen is > 100 ng/mL	>70 ng/mL

All phoned results are followed by mailed confirmation. All tests are screening tests. Abnormal results need full evaluation before a diagnosis is confirmed. Cut-off values are evaluated periodically and subject to change.

Confirmatory Testing and Management

Newborn screening tests are not diagnostic and MUST be confirmed by appropriate diagnostic testing.

Babies with elevated IRT will be referred to a Cystic Fibrosis Center for sweat test and often DNA confirmatory testing.

Treatment

Treatment is complex and multidisciplinary. Adequate nutrition is essential and is established by digestive enzyme replacement, fat-soluble vitamin supplementation, specialized diet. Vigorous respiratory care is also necessary. Acknowledgment of and regular evaluation for other complications are appropriate. Preventative and therapeutic interventions are best coordinated through a Cystic Fibrosis Team. Early treatment of CF has proved to be associated with improved weight gain and better control of respiratory condition.

Screening Practice Considerations

Detection of elevated IRT does not depend on protein or lactose ingestion and can be DONE reliably before protein feeding.

Over 1000 mutations have been identified at the CF locus and this has led to recognition of wide variability in the clinical features associated with the many mutations. Not all of the variant forms will be detected by IRT newborn screening.

ORGANIC ACIDURIAS

The organic acidurias are a group of inherited conditions, almost all autosomal recessive, in which excess amounts of organic acids accumulate in blood and other body fluids and are excreted in excess in the urine. The accumulated organic acids result in disturbances of the body's acid/base balance producing a metabolic acidosis. The acidosis may be associated with acute clinical manifestations such as lethargy, vomiting, seizures, disturbances in muscle tone, and alterations in level of consciousness. Chronic manifestations may include developmental delay, disturbances in growth and increased susceptibility to infection. Other metabolic pathways may be disrupted by the disturbance of organic acid metabolism resulting in hypoglycemia, hyperammonemia, abnormal liver function, and in some cases pancytopenia. Treatment is difficult and not always successful, but includes a protein-restricted diet, sometimes restriction of specific amino acid(s) and careful and complex preventive procedures. In some cases, carnitine or certain other medications are part of the therapy.

Screening for the organic acidurias is by MS/MS analysis of acylcarnitine derivatives of the various organic acids. Screening for some of the disorders is more sensitive after a protein feed, but sensitivity is high even with specimens obtained before full feeding.

There are a number of these disorders and there is variability within each disorder. Confirmation of diagnosis and effective treatment are complex and require referral to a metabolic center.

GLUTARIC ACIDEMIA I (GA I)

Glutaric Acidemia I (GA I) is an autosomal recessive disorder resulting from a deficiency in the enzyme glutaryl CoA dehydrogenase. The birth prevalence rate is estimated to be 1:100,000 births in the general population but is much higher among the Amish.

Clinical Features

The clinical presentation most commonly is a relatively sudden onset of vomiting and an acute encephalopathy manifested by seizures, athetoid movements, opisthotonic posturing and dystonia. Prior to the definitive symptoms there may have been macrocephaly, mild developmental delay and growth delay. There are characteristic findings on brain imaging, particularly in the basal ganglia. The onset of acute symptoms usually occurs at age 6-18 months and is often associated with an intercurrent illness. Cognitive function is usually relatively spared. During the acute episodes there may be hypoglycemia, ketoacidosis, and hyperammonemia. With early (before onset of encephalopathy) diagnosis and appropriate treatment, the neurologic manifestations can be prevented. There are other clinical presentations and occasionally children with the enzyme deficiency may be virtually asymptomatic.

Laboratory Test

There is elevation of the corresponding acylcarnitine detectable by MS/MS analysis of the blood spot. Various acylcarnitine are sometimes elevated in very low birth weight OR very ill newborns.

TABLE 11

Normal Values and Laboratory Criteria for Requesting Repeat Samples

ANALYTE	NORMAL	PHONE FOLLOW-UP	MAIL FOLLOW-UP
<i>Glutaryl</i> carnitine	< 0.16 $\mu\text{mole/L}$	$\geq 0.23 \mu\text{mole/L}$	0.16 - 0.23 $\mu\text{mole/L}$

All phoned results are followed by mailed confirmation. All tests are screening tests. Abnormal results need full evaluation before a diagnosis is confirmed. Cut-off values are evaluated periodically and subject to change.

Confirmatory Testing

Newborn screening tests are not diagnostic. Confirmation is by measurement of glutaric acid in the urine and by measurement of the enzyme in skin fibroblasts or by mutation analysis.

Treatment

Treatment includes prevention of metabolic stress, appropriate nutrition and administration of certain medications in some cases.

OTHER ORGANIC ACIDURIAS

A number of other organic acid disorders may be identified by MS/MS analysis of the blood spots. Clinical presentations vary, but most include acidosis and hypoglycemia and many have complications of ketosis and hyperammonemia. Most are considered to be rare, but it is possible that widespread screening may determine they are more common than previously thought. Some are summarized below:

TABLE 12

Organic Acidurias

DISORDER	LABORATORY METHOD	CLINICAL FEATURES
<i>Methylmalonic Acidemia (MMA)</i>	<i>Tandem Mass Spectrometry (MS/MS) for acylcarnitines. Primary marker Propionylcarnitine (AC3), Secondary Methylmalonylcarnitine (AC3-2M-DC)</i>	<i>Several forms, (some involving disorders of B 12 metabolism) - acidosis, ketosis, hypoglycemia, hyperammonemia, neonatal onset of seizures, lethargy</i>
<i>Propionic Acidemia (PA)</i>	<i>Tandem Mass Spectrometry (MS/MS) for acylcarnitines. Primary marker Propionylcarnitine (AC3)</i>	<i>Similar to MMA - Treatment may include biotin, carnitine, antibiotics to control bowel flora</i>
<i>Isovaleric Acidemia (IVA)</i>	<i>Tandem Mass Spectrometry (MS/MS) for acylcarnitines. Primary marker Isovalerylcarnitine (AC5)</i>	<i>Acidosis, moderate ketosis "Sweaty feet" odor</i>
<i>3-Methylcrotonyl-CoA Carboxylase Deficiency (3-MCC)</i>	<i>Tandem Mass Spectrometry (MS/MS) for acylcarnitines. Primary marker Hydroxyisovalerylcarnitine (AC5-OH)</i>	<i>Later onset; some asymptomatic. hypoglycemia, acidosis, low carnitine</i>
<i>3-Hydroxy-3-Methylglutaryl CoA Lyase Deficiency (HMG)</i>	<i>Tandem Mass Spectrometry (MS/MS) for acylcarnitines. Primary marker Hydroxyisovalerylcarnitine (AC5-OH), Secondary 3-Methylglutaryl carnitine (AC5-3M-DC)</i>	<i>Similar clinical picture No ketosis</i>
<i>Beta keto thiolase Deficiency (BKD)</i>	<i>Tandem Mass Spectrometry (MS/MS) for acylcarnitines. Primary marker Tiglylcarnitine (AC5:1), Secondary Hydroxyisovalerylcarnitine (AC5-OH)</i>	<i>Acidosis, ketosis Vomiting, irritability</i>
<i>2-Methylbutyryl-CoA Dehydrogenase Deficiency (2-MBCD)</i>	<i>Tandem Mass Spectrometry (MS/MS) for acylcarnitines. Primary marker Isovalerylcarnitine (AC5)</i>	<i>Rare, variable clinical presentations</i>
<i>Isobutyryl-CoA Dehydrogenase Deficiency (IBCD)</i>	<i>Tandem Mass Spectrometry (MS/MS) for acylcarnitines. Primary marker Butyrylcarnitine (AC4)</i>	<i>Rare, variable clinical presentations</i>
<i>Multiple Carboxylase Deficiency (MCD)</i>	<i>Tandem Mass Spectrometry (MS/MS) for acylcarnitines. Primary markers Propionylcarnitine (AC3), Hydroxyisovalerylcarnitine (AC5OH)</i>	<i>Acidosis, vomiting, irritability</i>

MAPLE SYRUP URINE DISEASE (MSUD)

Maple Syrup Urine Disease (MSUD) is an autosomal recessive disorder characterized by an inability to metabolize the branched chain amino acids, leucine, isoleucine and valine. The birth prevalence rate is approximately 1:100,000 births. MSUD is more frequent in certain populations including the Amish/Mennonite.

Clinical Features

MSUD, in the severe form, is associated with progressive neurological damage beginning within a few days of birth. A high-pitched cry, irritability, convulsions, spasticity, and central nervous system depression are presenting signs. If not treated, the disease leads to death in a few days to a few weeks. There is severe metabolic acidosis and usually hypoglycemia. Plasma leucine begins to rise usually within 24 hours of birth, and within a few days ketoacids appear in the urine. These impart a characteristic sweet maple syrup odor to the urine (and to ear wax) which gives the disease its name.

As with virtually all hereditary disorders, there are less severe variants, the mildest of which may go undetected for some time until some intercurrent illness unmasks the biochemical abnormalities.

Laboratory Test

Blood leucine is estimated by MS/MS. The leucine/phenylalanine ratio is also calculated. Normal leucine levels are $< 372 \mu\text{mole/L}$; even transient elevation of plasma leucine in the newborn is unusual, unless the infant is pre-term and/or receiving IV amino acid preparations.

TABLE 13

Normal Values and Laboratory Criteria for Requesting Repeat Samples

ANALYTE	NORMAL	PHONE FOLLOW-UP	MAIL FOLLOW-UP
<i>Leucine/Isoleucine</i>	$< 372 \mu\text{mole/L}$	$> 429 \mu\text{mole/L}$	$372 - 429 \mu\text{mole/L}$

All phoned results are followed by mailed confirmation. All tests are screening tests. Abnormal results need full evaluation before a diagnosis is confirmed. Cut-off values are evaluated periodically and subject to change.

Confirmatory Testing

Newborn screening tests are not diagnostic and **MUST** be confirmed by appropriate specific testing. Infants with suspected MSUD need **immediate** evaluation and usually hospitalization at a Tertiary Care Pediatric Hospital for confirmatory testing, treatment and consultation with a specialist in metabolic disease.

Treatment

Any infant in whom the plasma leucine is 429 umole/L or greater is considered to have MSUD until proven otherwise. Any infant suspected of having this disorder needs to be transferred to a major medical center as quickly as possible since investigation and management is complicated and death may occur rapidly in untreated cases.

Treatment, which must be continued for life, is a strict diet designed to control the intake of the branched chain amino acids. Treatment is difficult but outcome may be good.

Screening Practice Considerations

Sensitivity of testing for the severe forms is close to 100% when performed after 24 hours of protein feeding. Sensitivity is less when testing is performed prior to adequate feeding. Plasma leucine may be elevated, usually along with other amino acids, in babies receiving intravenous amino acid preparations (total parenteral nutrition - TPN - or hyperalimentation - HA). Various acylcarnitine are sometimes elevated in very low birth weight or very ill newborns.

HOMOCYSTINURIA AND OTHER DISORDERS OF AMINO ACID METABOLISM

The disorders of amino acid metabolism are a diverse group of conditions (mostly autosomal recessive) related to absence or deficiency of various enzymes involved in the processing of amino acids. The clinical manifestations and treatments are variable.

Homocystinuria is one of several autosomal recessive disorders of methionine metabolism, including deficiency of cystathionine beta synthase.

Clinical Features of Homocystinuria

Clinical manifestations are usually not present in the newborn period but develop throughout childhood. These include structural eye anomalies (including lens subluxation), characteristic habitus ("Marfanoid"), developmental delay (generally mild to moderate) and hypercoagulability.

Laboratory Test

MS/MS estimation of blood methionine (also elevated in primary hypermethioninemia).

Confirmatory Test

Quantitative blood amino acids, urine amino acids and enzyme quantitation.

Treatment

Diet; in some cases appropriate vitamin supplementation and anticipation of possible complications. With treatment outcome is expected to be good.

Screening Practice Consideration

MS/MS can also estimate levels of tyrosine, arginine, and citrulline identifying infants who may have one of the various forms of tyrosinemia, argininemia and citrullinemia. The latter two are disorders of the urea cycle. These are genetically complex and clinically heterogeneous disorders requiring prompt, detailed and complicated evaluation. Sensitivity and specificity of screening is still being determined. Treatment involves dietary management, in some cases medication. Outcomes may be variable but are believed to be improved with early diagnosis and prevention of the metabolic crises that may be part of these disorders. Various acylcarnitine are sometimes elevated in very low birth weight OR very ill newborns.

Ornithine transcarbamylase deficiency, the X-linked disorder of the urea cycle, is not currently identified by MS/MS.

TABLE 14

Amino Acid Disorders

DISORDER	LABORATORY METHOD	CLINICAL FEATURES
<i>Homocystinuria (HCYS)</i>	<i>Tandem Mass Spectrometry (MS/MS) for amino acids. Primary marker Methionine, Secondary Met/Phe ratio</i>	<i>Marfan habitus, eye anomalies, developmental delay, hypercoagulable. Onset of signs and symptoms is usually outside of infancy.</i>
<i>Tyrosinemia, several types (TYR)</i>	<i>Tandem Mass Spectrometry (MS/MS) for amino acids. Primary marker Tyrosine, Secondary Tyr/Phe ratio</i>	<i>Early onset of signs of liver disease, ascites, failure to thrive, jaundice, coagulopathy. (Type 1)</i>
<i>Argininemia (ARG)</i>	<i>Tandem Mass Spectrometry (MS/MS) for amino acids. Primary marker Arginine</i>	<i>Hyperammonemia syndrome with seizures, lethargy, coma. Infantile and later onset.</i>
<i>Citrullinemia (CIT) or Argininosuccinate Synthetase Deficiency (ASS)</i>	<i>Tandem Mass Spectrometry (MS/MS) for amino acids. Primary marker Citrulline, Secondary Cit/Arg ratio</i>	<i>Hyperammonemia with seizures, lethargy, coma in infancy. Later onset also described.</i>
<i>Argininosuccinate Lyase Deficiency (ASL)</i>	<i>Tandem Mass Spectrometry (MS/MS) for amino acids. Primary marker Citrulline, Secondary Cit/Arg ratio</i>	<i>Similar to ASS Deficiency</i>
<i>Hypermethioninemia (HMET)</i>	<i>Tandem Mass Spectrometry (MS/MS) for amino acids. Primary marker Methionine, Secondary Met/Phe ratio</i>	<i>Variable</i>

CARNITINE UPTAKE DEFICIENCY (CUD)

Carnitine Uptake Deficiency:

The birth prevalence rate of CUD occurs in about 1: 40,000 (not certain) CUD is a defect in membrane transport of carnitine. Carnitine is important in transport of fatty acids into the mitochondrial and therefore important in cellular energy metabolism.

Clinical Features

Children with CUD may present in infancy with signs and symptoms similar to those seen in infants with disorders of fatty acid oxidation including hypoketotic hypoglycemia, hyperammonemia and cardiomyopathy. Some children do not have symptoms in infancy but develop cardiomyopathy later in childhood. Sudden infant death has been described rarely.

Laboratory Tests

Confirmation is by measurement of Free Carnitine (C0) from a whole-blood dried blood spot.

TABLE 15

Normal Values and Laboratory Criteria for Requesting Repeat Samples

ANALYTE	NORMAL	PHONE FOLLOW-UP	MAIL FOLLOW-UP
Free Carnitine (C0)	> 6.0 $\mu\text{mol/L}$	< 5.0 $\mu\text{mol/L}$	5.0 - 6.0 $\mu\text{mol/L}$

All phoned results are followed by mailed confirmation. All tests are screening tests. Abnormal results need full evaluation before a diagnosis is confirmed. Cut-off values are evaluated periodically and subject to change.

Confirmatory Testing and Management

Newborn screening tests are not diagnostic and MUST be confirmed by appropriate diagnostic testing.

Treatment: Life long oral carnitine. Outcome is expected to be excellent if carnitine is taken reliably.

Screening Practice Considerations: Screening does not require protein feeding.

FATTY ACID OXIDATION (FAO) DISORDERS

The Fatty Acid Oxidation (FAO) disorders are a group of inherited disorders (all are autosomal recessive) in which affected individuals have a deficiency or absence of one of the many enzymes involved in the metabolism of dietary or stored fat. Fatty acids are metabolized during periods of relative fasting. If one of the enzymes is deficient there will be accumulation of certain fatty acids. MS/MS analysis of the blood spot generates a spectrum of the acyl carnitines of the various fatty acids and interpretation of the spectrum identifies fatty acids present in excess and suggests the diagnosis of one of the FAO disorders.

The clinical symptoms of the FAO disorders are variable as might be expected. Some present in infancy with hypotonia, lethargy, seizures, vomiting. Hypoglycemia often occurs. Ketosis is absent or minimal in some. Liver failure occurs in some, as does cardiomyopathy. A Reye Syndrome-like picture has been described in some affected children. It is believed that some cases of Sudden Infant Death Syndrome (SIDS) may be related to an undiagnosed FAO disorder.

MEDIUM CHAIN ACYL COA DEHYDROGENASE (MCAD) DEFICIENCY

Medium Chain Acyl CoA Dehydrogenase (MCAD) Deficiency is the most common of the FAO disorders. It is believed to occur in 1:15,000 live births.

Clinical Features

The clinical presentation is variable. Most commonly it presents in the first few years of life, in the context of a fast or an intercurrent infection, with lethargy, vomiting, seizures, and even coma. A Reye Syndrome-like picture has been described in some affected individuals. Hypoglycemia with hypoketonemia is characteristic. There may also be hyperammonemia, elevated uric acid, mild evidence of liver dysfunction, rhabdomyolysis and relatively mild acidosis. It is believed some affected individuals remain asymptomatic, perhaps because they never experienced a significant fast or intercurrent infection. It is also possible that some cases of SIDS may be related to an unidentified MCAD Deficiency.

Laboratory Test

Elevation of corresponding fatty acid acylcarnitines and characteristic acylcarnitine ratios detected by MS/MS. Testing is believed to be sensitive for detection of MCAD deficiency even if there has been no feeding. However, sensitivity appears to decrease after the first few weeks of life. Various acylcarnitine are sometimes elevated in very low birth weight OR very ill newborns.

TABLE 16

Medium Chain Acyl CoA Dehydrogenase (MCAD) Deficiency

ANALYTE	NORMAL	PHONE FOLLOW-UP	MAIL FOLLOW-UP
<i>Primary marker - AC8 (octanoyl Carnitine)</i>	<i>AC8 < 0.35 μmole/L</i>	<i>AC8 \geq 0.46 μmole/L</i>	<i>AC8, 0.35 - 0.45 μmole/L</i>
<i>Secondary markers - AC6 & AC10:1 (hexanoylcarnitine & decenoylcarnitine)</i>	<i>secondary marker significance varies</i>	<i>secondary marker significance varies</i>	<i>secondary marker significance varies</i>

All phoned results are followed by mailed confirmation. All tests are screening tests. Abnormal results need full evaluation before a diagnosis is confirmed. Cut-off values are evaluated periodically and subject to change.

Confirmatory Testing

Quantitation of acyl carnitines at a reference laboratory and/or mutation analysis, along with other appropriate metabolic studies, are confirmatory.

Treatment

Management of MCAD deficiency includes provision of adequate calories in all situations, particularly at time of intercurrent infection. Fasting is avoided. Carnitine supplementation is recommended. A diet low in long chain fatty acids may be helpful. With appropriate therapy and particularly with attention to prevention of complications an excellent outcome is expected.

TABLE 17

OTHER FATTY ACID OXIDATION (FAO) DISORDERS

DISORDER	LABORATORY METHOD	CLINICAL FEATURES
Short-chain Acyl-CoA Dehydrogenase Deficiency (SCAD)	Tandem Mass Spectrometry (MS/MS) for acylcarnitines. Primary marker Butyrylcarnitine (AC4), Secondary marker Isovalerylcarnitine (AC5)	Variable presentation, poor feeding, vomiting, hyperammonemia, ketosis, hypoglycemia; sometimes asymptomatic Adult form - weakness/myopathy
Very Long-Chain Acyl-CoA Dehydrogenase Deficiency (VLCAD)	Tandem Mass Spectrometry (MS/MS) for acylcarnitines. Primary marker Tetradecenoylcarnitine (AC14:1), Secondary marker Hydroxyhexadecanoylcarnitine (AC16-OH)	Neonatal lethargy, hypoglycemia, acidosis, hyperammonemia, hypoketotic. Cardiomyopathy
Long Chain Hydroxyacyl-CoA Dehydrogenase Deficiency (LCHAD) OR Trifunctional Protein Deficiency (TFP)	Tandem Mass Spectrometry (MS/MS) for acylcarnitines. Primary marker Hydroxyhexadecanoylcarnitine (AC16-OH)	Onset newborn to age 3 Vomiting, hypoketotic, hypoglycemia, striking increased CPK (rhabdomyolysis), cardiomyopathy, retinopathy. Maternal "HELPP"
Carnitine Palmitoyl Transferase Deficiency II (CPTII)	Tandem Mass Spectrometry (MS/MS) for acylcarnitines. Primary marker hexadecanoylcarnitine (AC16), Secondary marker Octadecenoylcarnitine (AC18:1)	3 forms: Neonatal, infant, adult
Glutaric Acidemia II (GA II) OR Multiple Acyl-CoA Dehydrogenase Deficiency (MADD)	Tandem Mass Spectrometry (MS/MS) for acylcarnitines. Multiple Primary markers: Butyrylcarnitine (AC4), Isovalerylcarnitine (AC5), Octanoylcarnitine (AC8), Decenoylcarnitine (AC10), Hexadecanoylcarnitine (AC16), Glutarylcarnitine (AC5-DC)	At least 3 forms: Neonatal with anomalies, neonatal without anomalies, late onset;
Carnitine/Acyl Carnitine Translocase Deficiency (CAT)	Tandem Mass Spectrometry (MS/MS) for Acylcarnitines. Primary marker Hexadecanoylcarnitine (AC16) Secondary marker Octadecenoylcarnitine (AC18:1)	Hypoglycemia, weakness, myopathy
Carnitine Uptake Deficiency (CUD)	Tandem Mass Spectrometry (MS/MS) for Acylcarnitines. Primary marker Free Carnitine (CO)	

SCREENING FORM INFORMATION

The Newborn Screening Program Specimen Collection Form is used for all newborn screening tests. Only a standardized, quality tested type of filter paper can be used for specimen submission. **Please note: forms are precoded for the specific individual/facility; they must not be lent to, or borrowed from other units or facilities.**

Filter paper expiration date: The filter paper (card) for newborn screening blood collection has a shelf life of two years. Please check the filter paper for expiration date. If specimen was collected on expired filter paper, specimen will be unsatisfactory for testing and a repeat collection will be requested.

Forms may be obtained from the Delaware Division of Public Health Laboratory by **EMAIL** request: LabSupplies@state.de.us, by **FAX** request: **302-653-1928** or by **PHONE** request: **302-223-1470**, Laboratory Shipping and Receiving.

Supplies can also be ordered by completing the Delaware Newborn Screening Supply Request Form. To request copies of this form please call (1-800-262-3030).

When ordering specimens forms, please allow 7-10 days for preparation and shipping. All specimen forms are precoded for the specific facility for submission.

Brochures, hospital parent letters, specimen tracking forms, refusal forms and drying racks can be obtained by **EMAIL** request: Linda.Braxton-Webb@state.de.us or by **FAX** request: **302-741-8576** or by **PHONE** request: **302 741-2990** or toll free at **1-800-262-3030**, from the Delaware Division of Public Health, Newborn Screening Program, 417 Federal Street, Dover, DE 19901.

COMPLETION OF THE SPECIMEN FORM

Complete **ALL** information requested on specimen form. Please **PRINT** when completing specimen form, **USE PEN**. The form consists of the original and three copies; please press hard when **PRINTING**. The blue copy that extends over the filter paper (**submitter copy**) is to be removed following completion of the information and retained in the medical record.

ALL information must be provided on the specimen form regardless of which specimen is being obtained (initial or repeat). Failure to do so makes it difficult to track the infant's results. Patient information is **critical** for rapid follow-up.

Data which are critical include: Baby name, birthdate/birth time, birth weight, feeding date/feeding time, feeding status, specimen date/specimen time, specimen taken by, unit at hospital where specimen was taken (**some hospitals have several units**), information regarding transfusion status, parent address and phone information as well as name of **pediatrician after discharge**.

Other important information:

Adoption/Foster Care/Correctional Facility: If baby is being adopted, in foster care or mother is in a Correctional Facility, please provide the adoption agency/foster care/Correctional Facility information, name, address, phone and contact information in the address section of the specimen form. Contact information to locate the baby is important to provide follow-up for abnormal test results.

Previous studies of NSP forms have indicated up to 20% of specimens were missing important patient data. For example, 2% did not list the infant's name, or it was unreadable. In the event of an abnormal result, such specimen forms would be difficult and time consuming to match to the correct infant.

Imprinting machines (addressograph machines) which use plastic cards to stamp the infant's name on the request commonly produce unreadable forms and may contaminate the filter paper.

Refer to Table 18, page 39 for detailed specimen form completion instructions.

TABLE 18
SPECIMEN FORM COMPLETION INSTRUCTIONS

FIELD	DIRECTIONS
FIRST SPECIMEN	Check box if first/original blood screening specimen.
SECOND SPECIMEN	Check this box for routine second specimen.
OTHER	Check this box if repeat is requested for abnormal or unsatisfactory previous specimen.
BABY'S NAME	PRINT complete name of infant, Last Name then First Name.
SEX	Circle one - Male or Female
BIRTH DATE	Write date of birth.
TIME OF DAY	Write time of birth. Indicate if time is 24 hr (military) or am/pm.
BIRTH WEIGHT	Write birth weight in pounds and ounces or grams. (Not kilograms)
BIRTH ORDER	Check if Multiple Birth then enter A, B, C etc. to show birth order of baby.
INFANT'S AGE AT TIME OF COLLECTION	Check either the < 24 hours or > 24 hours box to indicate whether baby was under or over 24 hours of age at the time specimen was collected.
GEST. AGE AT BIRTH	Give gestational age at birth in weeks.
MED. REC.	Enter baby's hospital medical record number; used to file results in patient chart when received from the laboratory.
SPECIMEN DATE	Write date blood specimen was drawn.
SPECIMEN TIME OF DAY	Write time blood specimen was drawn and circle whether it was in AM, PM, or 24 hr. time.
SPECIMEN TAKEN BY	PRINT first initial and complete last name of person performing test.
UNIT / DEPT.	Enter unit or department where specimen was taken (SCN, Cardiac, Lab, etc.)
FEEDING LAST 24 HOURS	Check food source received in last 24 hours. For Enfamil, need to know if Soy or Lactose.
RACE / ETHNICITY	Check all boxes that apply according to parental information.
TRANSFUSION, RBC	Check box if baby was transfused and enter the latest transfusion date.
HYPERALIMENTATION (TPN)	Check box if baby is on Hyperalimentation (HA) or Total Parenteral Nutrition (TPN) and enter the start and end dates. TPN/HA is acceptable as protein source for newborn screening tests.
HOSPITAL / CODE	On hospital forms this block contains a pre-coded label with hospital name and code. On forms with no pre-coded label, complete with hospital name and code number. This is used to report results back to infant's medical records at the hospital of birth.
PEDIATRICIAN / CODE	Enter name of the physician/clinic (AND/OR code number) whom the mother plans to use for baby's follow-up care. This is used to report results to the primary care provider and for follow up. If the infant is in a Neonatal Intensive Care Unit, write the neonatology unit code.
MOTHER'S NAME	Print complete name of mother - Last Name then First Name.
ADOPTION AGENCY	Enter name of Adoption Agency and telephone number.
MOTHER'S ADDRESS	Print complete street address, apartment number, city, state and zip.
PHONE NUMBER	Write mother's home phone, including area code. If parent has no phone, obtain a message phone number or a relative's phone number where parent may be contacted for abnormal test results.
MOTHER'S AGE	Write mother's current age.
HEPATITIS B	Indicate injection given and date. This form will be forwarded to the Office of Immunization for entry into the Immunization Record.
HEARING SCREENING	Check screening method and date done. Check correct box for each ear - Passed or Failed. Check reason if screening was not done. Check all Hearing Risk Factors.

NEWBORN SCREENING PROGRAM REQUIREMENTS

INFORMATION TO FAMILIES ABOUT NEWBORN SCREENING

Each pregnant woman shall receive education related to the screening, to include the reason for screening, procedure and schedule, as well as receive a Newborn Screening Program brochure.

The person or facility responsible for providing the newborn screening information shall be, in order of responsibility:

- The health care facility or practitioner responsible for care of the pregnant woman;
- The health care provider providing childbirth education classes;
- The hospital, birthing facility, or other health care facility, or practitioner responsible for obtaining the blood spot specimen.

Information about the Newborn Screening Program and brochure is available from the Newborn Screening Program Office, 1-800-262-3030.

Program Requirements: A specimen for newborn screening shall be collected prior to hospital discharge, but no later than 3 days after birth from every infant surviving more than two days, as follows:

- (1) In the case of infants born outside a hospital or other health care facility and of infants who will remain in the hospital or health care facility for 24 hours of milk feedings or more, a specimen shall be collected not sooner than 24 hours after the onset of milk feeding, but no later than **3 days after birth**, preferably between **36 and 72 hours after birth**. A second specimen is to be collected between **7 and 28 days of age**.
- (2) Pre-term or sick newborns may have the initial screen as late as **3 days of age**. The second screen on pre-term or sick newborns is to be done at hospital discharge, or at **28 days of age**.
- (3) In the case of infants discharged from a hospital or other health care facility before 24 hours of milk feedings, (early testing) a specimen shall be obtained immediately prior to discharge from the facility, and a second specimen shall be collected from such infants after **72 hours of age and before 14 days of age**.
- (4) **TESTING BEFORE TRANSFER OF INFANT TO ANOTHER UNIT**
Delaware Newborn Screening Regulations, page 3, Section IV, specify that infants who are transferred from one newborn unit to another unit within 48 hours of birth should be tested by the receiving facility.
- (5) Babies who are being fed intravenously with amino acid solution (TPN or HA) often have elevated levels of amino acids (leucine, methionine, phenylalanine, arginine, etc.). Prompt repeat screen will be requested on these babies - the screening to be done 48 hours after intravenous feeding has been discontinued.

SPECIMEN TIMING

The Hospital or other health care facility is responsible for providing the mother with information on when and where to return for the repeat specimen. The repeat specimen is collected using the timing as described in Table 19.

TABLE 19

SPECIMEN TIMING

	FIRST SPECIMEN	SECOND SPECIMEN
<i>EARLY TESTING</i>	<i>< 24 hours of milk feeding</i>	<i>72 hours - 14 days of age</i>
<i>STANDARD TESTING</i>	<i>> 24 hours of milk feeding to 3 days of age</i>	<i>7 days - 28 days of age (later specimens will be accepted)</i>
<i>PRE-TERM OR SICK INFANT TESTING</i>	<i>By 3 days of age</i>	<i>At hospital discharge or at 28 days of age</i>

Transfusion - If a baby has a transfusion before the initial screen is obtained the second screen should still be obtained according to schedule above. However, a final screen will need to be obtained **90 days** after last transfusion so that an accurate assessment of hemoglobins can be assured.

SPECIMEN COLLECTION INFORMATION

1. Explain the Newborn Screening Test procedure to the parent(s) and give them a copy of the Newborn Screening Program brochure. To request a copy of the Delaware Newborn Screening Program brochure, call (1-800-262-3030).
2. Obtain a specimen from **EVERY** infant, according to the timing schedule described on previous page.

SPECIMEN COLLECTION

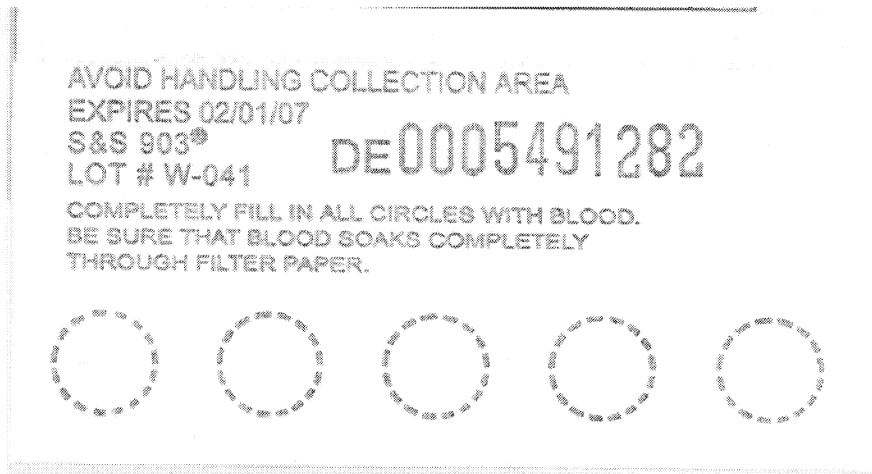
1. Use only the blood collection specimen form for newborn screening blood collection provided by the Delaware Newborn Screening Program. **CAUTION:** Avoid handling the blood collection end of the filter paper card before, during or after collection since skin oils may alter absorption of blood and contaminate the specimen.
2. Warm infant's heel for about 3 minutes with a moist towel (temperature no higher than 42°C) to increase blood flow, and hold foot in a position to increase venous pressure.
3. Select a puncture site and wipe infant's heel with 70% isopropyl alcohol (not Betadine) and allow to air-dry thoroughly. (**CORD BLOOD IS NOT A SATISFACTORY SPECIMEN.**) Samples obtained from peripheral or central lines are acceptable, provided that the line is not being used for hyperalimentation or for antibiotics.) Heel stick blood is the preferred method of collection.
4. Puncture the infant's heel on the plantar surface with a sterile lancet or with a heel incision device (Tenderfoot is recommended). Any puncture device used should be selected so the puncture does not exceed 2.0 mm in depth. For worker safety disposable skin puncture devices that protect the user from unintentional self-inflicted skin punctures should be used.
5. Wipe off the first drop of blood with sterile gauze or cotton ball since it may contain tissue fluids which may dilute sample.
6. Allow the second drop to form by spontaneous free flow of blood.
7. Touch the filter paper gently against the large blood drop and, in one step, allow a sufficient quantity of blood to soak through and completely fill the pre-printed circle. **Do not press the filter paper against the puncture site on the heel.** Apply blood to only one side of the filter paper. Blood should soak all the way through the paper such that the blood spots look similar on both sides. **DO NOT APPLY BLOOD TO BOTH SIDES.** Both sides of the filter paper should be examined to assure that the blood uniformly penetrated and saturated the filter paper. Complete saturation of the entire circle is essential for accurate testing.
8. It is important **NOT** to superimpose the blood drops on top of each other. Let each drop touch the paper about 1/8 inch away from the previous one. This prevents layering on the paper, which is one cause of unsatisfactory results.

9. **Collect the blood in all five circles.** A minimum of four circles is necessary to complete the test battery. If there are problems obtaining an adequate quantity of blood, it is better to fill four circles completely, than to fill five circles inadequately.
10. After the specimen has been collected, elevate the infant's foot and using sterile gauze, briefly apply gentle pressure to the puncture site until the bleeding stops.
11. Allow blood specimen to **AIR DRY COMPLETELY** in a horizontal\level position on a non-absorbent surface, such as a specimen drying rack (drying racks can be obtained from the Newborn Screening Program Office) for a minimum of 3 hours at ambient temperature. Do not stack specimens. Do not dry on a heater, microwave or put in a hot mailbox over the weekend.
12. Remove **BLUE SUBMITTER COPY** (copy that covers filter paper portion) for inclusion into medical record.
13. If courier pickup is available, insert dried sample into specimen pickup envelope and place in designated pick-up spot.

Contact the Newborn Screening Program Office at 302-741-2990 or toll free 1-800-262-3030) for additional information and assistance with specimen collection.

*Specimen collection instructions are consistent with the recommendations in Blood Collection on Filter Paper for Newborn Screening Programs; Approved Standard-Fourth Edition. National Committee for Clinical Laboratory Standards, (NCCLS), Vol. 23, No. 1=21 [NCCLS Document LA4-A4].

For more information refer to Whatman publication, "Neonatal Screening, Blood Specimen Collection and Handling Procedure", following two pages.



WARNING

Newborn Screening Expired FILTER PAPER

Please check your newborn screening specimen forms for filter paper expiration date on each card before specimen collection.

The expiration date is located on the NEWBORN SCREENING FILTER PAPER WHERE THE 5 CIRCLES ARE.

The filter paper (card) for newborn screening blood collection has a shelf life of two years. If a specimen was collected on expired filter paper, the specimen will be unsatisfactory for testing and a repeat collection will be requested.

Contact the Newborn Screening Program with questions at:
1-800-262-3030 or (302) 741-2990 or Email: Betsy.Voss@state.de.us

Please send any expired forms back to the Newborn Screening Program Office at address listed below:

417 Federal Street
Dover, DE 19901

POOR QUALITY SPECIMENS

Poor quality specimens, also referred to as “Hand Punch” specimens, are those specimens that exhibit traits that might cause the specimen to be rejected. These specimens did have sufficient blood for laboratory personnel to pick and choose enough places on the DBS to perform all of the required testing, and did not have to be rejected. Most required “hand punching” to work around the poor areas. Because the sample used for testing is just a 1/8” circle of blood infused paper, it is of extreme importance for the blood to be collected properly and saturated fully but not over-saturated. The most common reasons cited for poor quality include:

- Circles not filled
- Incomplete Saturation (not saturated through to back of paper)
- Insufficient Application (lots of tiny drops)
- Over saturation (double application of blood)
- Serum rings (squeezing too hard)
- Damaged (paper torn, ripped)
- Contaminated (foreign substance on card, got wet)

Filter paper expiration date: The filter paper (card) for newborn screening blood collection has a shelf life of two years. Please check the filter paper for expiration date. If specimen was collected on expired filter paper, specimen will be unsatisfactory for testing and a repeat collection will be requested.

Please refer to previous page “Simple Spot Check.”

SPECIMEN TRANSPORT TRACKING

In December 2000 members of the technical review team of the National Newborn Screening and Genetics Resource Center (NNSGRC) issued a commendation to the Delaware Newborn Screening Program for its courier transport system. The adoption of a courier system has resulted in an improved turnaround time from date of sample collection to date of screening result availability. However, the review team also strongly recommended that the Delaware NSP initiate a specimen tracking system for the newborn screening blood specimens. They emphasized the importance of:

- Documentation of collection of each specimen by the submitting hospitals;
- Documentation of the pickup of each specimen by the courier; and
- Documentation of safe transport of each specimen to the receiving laboratory.

During the year following the visit from the NNSGRC the Newborn Screening Program devised and tested a specimen tracking system. This system is presently used in all birth facilities.

Each facility has individual tracking sheets. Refer to Sample Tacking Form, page 41. Facility staff completes the tracking forms using the tracking labels from the specimen forms or by writing the requested information on the tracking form. Hospital staff verifies the specimens with the tracking sheet and places both the tracking sheet and the dried blood spot specimens together in the newborn screening specimen pick-up envelope.

When specimens are received at the testing laboratory, the specimen envelopes are logged in and the contents of the envelope are checked to verify there is a specimen for every infant listed on the tracking sheet. The tracking sheets are delivered daily to the Newborn Screening Program Office and checked for discrepancies.

To request specimen tracking forms please call 302-741-2990, or toll free at 1-800-262-3030.

DELAWARE NEWBORN SCREENING ■ SPECIMEN TRACKING SHEET
 Submitter Name: Hospital Date: ENTER CURRENT DATE

#	Baby's Name	Date of Birth	NSP Lab Use
1	Smith, John DE*003500000* <u>PLACE LABEL HERE</u>	9/1/06	
2	<u>PLACE LABEL HERE</u>		
3	<u>PLACE LABEL HERE</u>		
4	<u>PLACE LABEL HERE</u>		
5	<u>PLACE LABEL HERE</u>		
6	<u>PLACE LABEL HERE</u>		
7	<u>PLACE LABEL HERE</u>		
8	<u>PLACE LABEL HERE</u>		
9	<u>PLACE LABEL HERE</u>		
10	<u>PLACE LABEL HERE</u>		

SAMPLE

**MAILING INSTRUCTIONS
(FOR SPECIMENS NOT COLLECTED BY NSP LAB COURIER)**

1. Remove **BLUE SUBMITTER COPY** (copy that covers filter paper portion) for inclusion into medical record.
2. Obtain blood on filter paper.
3. Allow specimen to completely dry (for a minimum of 3 hours).
4. If mailing specimen, place dried specimen in mailing envelope, seal, and mail blood specimen to the Delaware Public Health Laboratory within 24 hours of collection using the mailing instructions below. If sample(s) cannot be mailed because of a Sunday or holiday, it is better to store in a cool room and send by express mail.
5. **DO NOT BATCH SPECIMENS COLLECTED ON SEPARATE DAYS.** All specimens should be placed in specimen pickup envelope within 24 hours of collection. If there is no courier pickup at your location please mail specimens **FIRST CLASS** or **EXPRESS MAIL**.

**DELAWARE PUBLIC HEALTH LABORATORY
30 SUNNYSIDE ROAD
SMYRNA, DELAWARE 19977
(302) 223-1470**

Specimens **MUST BE SENT WITHIN 24 hours of collection.** If sending by mail use **FIRST CLASS MAIL** or **EXPRESS MAIL**.

Check the mail system in your facility to insure prompt delivery of the specimen if using First Class mail. Specimens older than seven (7) days from collection date are **unsatisfactory** for testing and a repeat collection will be requested.

PARENT REFUSAL OF NEWBORN SCREENING TESTING

If the parents refuse the newborn screening test because the screening tests conflict with their religious tenets or practices, they must sign a "Newborn Screening Refusal Form". The completed refusal form and a newborn screening blood collection specimen form with demographic information on the infant must be returned to the Newborn Screening Program Office, Jesse S. Cooper Bldg., P.O. Box 637, Dover, DE 19903. The specimen collection envelope may be used to send the refusal forms to the Newborn Screening Program Office. A copy of the completed refusal form should be placed in the infant's medical record. To request refusal forms please call the Newborn Screening Program Office at 302-741-2990 or toll free 1-800-262-3030.

In the event a religious exemption is claimed from the requirements for newborn screening testing, the person who would otherwise be responsible for submitting the specimen for testing shall be responsible for submitting a completed affidavit, signed by the infant's parent(s). See below:

1. (I) (We) (am) (are) the (parent(s)) (legal guardian (s)) of _____ (name of child), _____(date of birth)
2. (I) (We) hereby (swear) (affirm) that (I) (we) subscribe to a belief in a relation to a Supreme Being involving duties superior to those arising from any human relation.
3. (I) (We) further (swear) (affirm) that our belief is sincere and meaningful and occupies a place in (my) (our) life parallel to that filled by the orthodox belief in God.
4. This belief is not a political, sociological or philosophical view of a merely personal moral code.
5. This belief causes (me) (us) to request an exemption from the requirements for testing for Hereditary Disorders by the Delaware Newborn Screening Program for _____ (name of child).

Signature of Parent (s) or Legal Guardian(s)

SWORN TO AND SUBSCRIBED before me, a registered Notary Public,
this ____ day of _____, 20__.

Notary Public (Seal)

My Commission Expires:

FEE EXEMPTION REQUEST

Parents of a newborn may be excused from payment of fees for newborn screening if the parents are unable to pay for the test. To request Fee Exemption forms please call 302-741-2990 or toll free 1-800-262-3030.

In the event a fee exemption claimed, the person otherwise responsible for submitting the specimen for testing shall be responsible for submitting a completed fee exemption form to the Delaware Newborn Screening Program Office, signed by the infant's parents, using the following language:

NEWBORN SCREENING PROGRAM STATEMENT OF FEE EXEMPTION

The undersigned states that the parents of

Print Name

Date of Birth

are unable to pay the fee for newborn screening testing for metabolic and hemoglobin disorders because of lack of funds.

Signature of Parent or Guardian

Print Name

Date

Witness

Date

Received in Newborn Screening Program Office: _____

Verified _____

REPORTING OF RESULTS

Before discharge, hospital and birth unit personnel will list on the NSP form the physician or clinic who will follow the child after discharge. In the event of an abnormality, the Newborn Screening Program must refer to this identified physician-of-record even though in some cases the infant is no longer under his or her care and may not even be known to him or her.

In the event that the results of an infants screening test are not received from the Laboratory within two weeks of collection, the hospital and practitioner must assume responsibility for follow-up. We recommend the following procedure:

1. Contact the Delaware Division of Public Health, Newborn Screening Program Office at **302-741-2990** or **TOLL FREE 800-262-3030** to determine if the specimen was received and to request a report.
2. If the specimen was not received, it must be presumed lost. Notify the infant's primary care provider or parents by phone or letter that the specimen may have been lost and that another should be obtained without delay.
3. Document these actions in the infant's medical record.

It is important for primary care providers to know the screening status of every infant in their care. Specimen collection should be documented both in the infant's chart and in a separate logbook. Information should include the name of the infant, hospital ID number, screening kit ID number, date collected, date picked up by the courier or 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 filed in the medical records. For every infant there must be a procedure for follow-up by the practitioner in case a result is not received. It is the responsibility of the health care facility where the infant is born or to which the infant is transferred and the newborn's primary care provider to ensure that every infant is tested and that a result is received and filed in the medical record. Primary care providers must also ensure that the second specimen is obtained at the appropriate time.

EDUCATIONAL SERVICES

The charge for newborn screening testing for Delaware babies includes an amount for educational activities to improve the quality of the screening practices within the state.

Screening Practice Surveillance Program

To assist hospitals, birth facilities and individual practitioners, the laboratory and the follow-up program office monitors the screening practices (transit time, inadequate specimens, demographic omissions and timing errors). Screening Practice Profiles (QA reports) are provided on a monthly basis to hospitals and birth facilities.

Hospitals, Birth Facilities, and Practitioners

In-services can be provided at your facility by program staff. These presentations cover any (or all) aspects of the screening program depending on your needs.

A 20-minute videotape demonstration showing correct collection procedures, problems and questions is available during presentations.

INFORMATION

For additional information, copies of materials, questions or comments regarding the practitioner's manual, please contact:

Newborn Screening Program
Division of Public Health
417 Federal Street
Dover, DE 19901

Telephone: (302) 741-2990
Toll Free: (800) 262-3030
Fax: (302) 741-8576

Delaware Public Health Laboratory
30 Sunnyside Road
Smyrna, DE 19977
(302) 223-1520

APPENDICES

Acknowledgements:

The Delaware Newborn Screening Program would like to acknowledge the valuable resource information provided in documents produced by the Newborn Screening Task Force, which was sponsored by the federal Health Resources and Services Administration (HRSA), the American Academy of Pediatrics (AAP), the National Newborn Screening and Genetics Resource Center (NNSGRC), the Council of Regional Genetic Services Network (CORN), the Medical Society of Delaware, and Whatman, Inc.

APPENDIX A

Regulations Pertaining to the Testing of Newborn Infants for Metabolic Hematologic and Endocrinologic Disorders

State Board of Health Regulations originally adopted July 14, 1994

Revised 2004

TITLE 16 DELAWARE ADMINISTRATIVE CODE

1
Department of Health and Social Services
Division of Public Health
Statutory Authority: 16 Delaware Code, Section 122(1) & (3)h (16 Del.C. §122(1) & (3)h)
29 Delaware Code, Section 7904 (29 Del.C. §7904)

107 REGULATIONS PERTAINING TO THE TESTING OF NEWBORN INFANTS FOR METABOLIC, HEMATOLOGIC AND ENDOCRINOLOGIC DISORDERS

Under the authority granted to the Department of Health and Social Services, Division of Public Health under 16 Del. C. sec 122 (1), 16 Del.C. sec. 122 (3) (h), and 29 Del.C. sec 7904 the Department of Health and Social Services, Division of Public Health, State of Delaware adopts the following regulations pertaining to the testing of newborns for various disorders.

PURPOSE: These regulations describe the Newborn Screening Program administered by the Delaware Division of Public Health. Under the authorization of the statues listed above, each newborn delivered in the state must be provided a panel of screening tests to identify certain metabolic, hematologic and endocrinologic disorders that may result in developmental delay, mental retardation, serious medical conditions, or death.

These regulations clarify responsibilities among the parties involved.

These regulations apply to each newborn infant born in the State. The responsibility for implementation of the regulations rests with the institution in which the infant is born, or if an infant is born outside an institution, with the person required to prepare and file the certificate of birth and with the newborn's primary care provider.

1.0 DEFINITIONS

"Blood specimen for metabolic, hematologic and endocrinologic disorders" means a dried blood spot on a special filter paper utilized for screening (not diagnostic) tests to establish the likely presence of certain metabolic, hematologic or endocrinologic disorders.

"Newborn infant" means any infant born in the state who is under 4 weeks of age.

"Metabolic disorder" means a disorder caused by a genetic alteration, which results in a defect in the structure or function of a specific enzyme or other protein. These disorders include, but are not limited to, Phenylketonuria (PKU), Galactosemia, Maple Syrup Urine Disease (MSUD), and Medium Chain Acyl-CoA Dehydrogenase (MCAD) Deficiency.

"Endocrinologic disorder" means the absence or deficiency of a hormone resulting in interference with normal health, growth or development. These disorders include Congenital Hypothyroidism (CH) and Congenital Adrenal Hyperplasia (CAH).

"Hematologic disorder" means, in these regulations, a condition in which a variation in one or more of the hemoglobin structural genes or in one or more of the genes involved in hemoglobin synthesis produces a variation in hemoglobin structure or synthesis, which result in variation in hemoglobin function. The term "hemoglobinopathies" includes sickle cell anemia, sickle cell hemoglobin C disease (SC disease), sickle beta thalassemia, beta thalassemia, alpha thalassemia, hemoglobin C disease and other clinically important variations in hemoglobin structure or synthesis.

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“Kit” means any or all parts of the combined materials, laboratory filter paper specimen forms, lancets, envelopes, Newborn Screening Program brochure, and/or other components provided by the State Newborn Screening Program for the purposes of collection of the blood spot specimen and for submission of the blood spot specimen for laboratory testing.

“Satisfactory specimen” means a blood spot specimen on which an accurate laboratory analysis for the various disorders can be performed.

“Unsatisfactory specimen” means a blood spot specimen which is of insufficient quantity; or a blood spot specimen on which an accurate analysis for the various disorders cannot be performed.

“IMF” stands for Insufficient Milk Feeding, which [means that insufficient time had passed (24 hours) between the time of the first milk feeding and the time at which the bloodspot specimen was obtained] is an inadequate time frame for milk feedings (<24 hours) prior to obtaining the blood spot specimen.

“Designated laboratory” is the laboratory or laboratories, which have been selected by the Division of Public Health to perform these services.

“The Newborn Screening Advisory Committee” means a committee, established through the Division of Public Health Newborn Screening Program, convened to provide advice and guidance to the Newborn Screening Program. Members include, but are not limited to: individuals or parents of individuals with one of the disorders for which screening is performed; physicians not employed by the Division of Public Health who have expertise in the disorders for which screening is performed; an attorney not employed by the Division of Public Health; an ethicist not employed by the Division of Public Health; representatives of relevant agencies within the Department of Health and Social Services. The Committee meets at least semi-annually. The Director of the Division of Public Health will appoint members after recommendation by the Newborn Screening Program.

2.0 DETERMINATION OF REQUIRED SCREENS

2.1 The Director of the Division of Public Health or designee shall determine what disorders will be tested for.

3.0 PERSONS RESPONSIBLE FOR SUBMITTING BLOOD SPOT SPECIMENS FOR SCREENING FOR METABOLIC, HEMATOLOGIC AND ENDOCRINOLOGIC DISORDERS

3.1 The person or institution responsible for assuring that a satisfactory blood spot specimen is submitted for testing newborns for metabolic, hematologic and endocrinologic disorders shall be, in order of responsibility:

- 3.1.1 the hospital, birthing facility or other licensed health care facility in which the newborn is born.
- 3.1.2 the newborn’s primary care provider; or, if no provider is identified;
- 3.1.3 the parent or legal guardian.

3.2 In cases of newborns entering a health care facility before 48 hours of age as result of transfer from another facility or of an infant not born in a hospital or other licensed health care facility, the receiving facility shall be responsible for the timely collection of the blood spot specimen.

TITLE 16 DELAWARE ADMINISTRATIVE CODE

4.0 MANNER OF SUBMITTING BLOOD SPOT SPECIMENS

4.1 All dried blood spot specimens submitted to the designated laboratory for testing shall be collected using kits available from the Newborn Screening Program office and/or designated laboratory.

4.2 Blood spot specimens collected for testing shall be forwarded from the institution at which the specimen is collected to the designated laboratory within 24 hours of collection, either by the designated Division of Public Health courier or by mail.

5.0 TIMING OF COLLECTING THE BLOOD SPOT SPECIMEN FOR SCREENING INFANTS

5.1 A blood spot specimen for screening for metabolic, hematologic, and endocrinologic disorders shall be collected prior to hospital discharge, but in no event later than 3 days after birth from every newborn infant as follows:

5.1.1 For infants born outside of a hospital or other health care facility a specimen shall be collected not sooner than 24 hours after the onset of milk feeding, but no later than 3 days after birth, preferably between 36 and 72 hours of birth. A second specimen is to be collected between 7 and 28 days of age.

5.1.2 For infants who are born in a hospital or health care facility or who are born outside and transferred into the hospital and who will remain in the hospital for 24 hours of milk feedings or more a blood spot specimen shall be collected not sooner than 24 hours after the onset of milk feeding, but no later than 3 days after birth, preferably between 36 and 72 hours after birth. A second blood spot specimen is to be collected between 7 and 28 days of age.

5.1.3 For pre term or sick newborns, the initial blood spot specimen may be collected as late as 3 days of age and must be collected no later than 3 days regardless of birth weight, illness or nutritional status. The second dried blood spot specimen on preterm or sick newborns is to be done at hospital discharge or 28 days of life which ever comes first.

5.1.4 When an infant is discharged from a hospital or other health care facility before 24 hours of milk feedings a blood spot specimen shall be obtained immediately prior to discharge from the facility and a second dried blood spot specimen shall be obtained after 3 days of age and before 14 days of age.

6.0 PROCEDURES FOR FOLLOW UP OF DRIED BLOOD SPOT SPECIMENS THAT WERE OBTAINED PRIOR TO 24 HOURS OF MILK FEEDING (IMF) AND FOR THOSE WHOSE RESULTS ARE DESIGNATED AS ABNORMAL OR SUSPICIOUS

6.1 The hospital or institution of birth or the hospital to which a newborn is transferred shall develop adequate procedures to insure that a satisfactory blood spot specimen is collected by the time each newborn is 2 weeks old from each newborn who is described by one or more of the following categories:

6.1.1 a newborn that is discharged from the institution prior to 24 hours of milk feedings (IMF).

6.1.2 a newborn on which the blood spot specimen is reported by the laboratory as "unsatisfactory".

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6.2 The hospital or institution of birth, the hospital to which a newborn is transferred and the primary care provider of the newborn shall cooperate with the Newborn Screening Program in completing follow up of newborns whose blood spot specimen result is designated as "abnormal" or "suspicious." This cooperation shall include:

- 6.2.1 providing appropriate demographic information to the Newborn Screening Program as requested on each baby whose blood spot specimen result is designated as "abnormal" or "suspicious."
- 6.2.2 providing the Newborn Screening Program with clinical information on each newborn as necessary for interpretation of the results of the testing of the blood spot specimen.

7.0 REPORTING OF RESULTS OF NEWBORN SCREENING TESTS

7.1 The designated laboratory shall report the results to the Newborn Screening Program as designated in the contract. All test results shall be available to the parent upon request through the birth hospital medical record department or their primary health care provider.

8.0 CONFIDENTIALITY OF RECORDS

8.1 The Newborn Screening Program shall maintain and treat as confidential all newborn screening communications with institutions, families and health care providers. The Newborn Screening Program shall maintain and treat as confidential a record of every newborn in whom a diagnosis of one or more of the various metabolic, hematologic, or endocrinologic disorders is confirmed.

8.2 Information may be disclosed by the Newborn Screening Program in summary forms, which do not identify individuals. Individuals or institutions requesting summary data must submit a proposal to the Newborn Screening Program and to the Institutional Review Board of the Division of Public Health.

9.0 FEES FOR NEWBORN SCREENING TESTS PERFORMED IN THE DESIGNATED LABORATORY

9.1 The Division of Public Health Newborn Screening Program shall bill the institution or individual for services provided to the institution or individual for each newborn screened under these regulations including but not limited to, the cost of the kits for collection of specimens, the laboratory fee for analysis, and administrative costs. The fee will be determined annually (in July) based on cost of the program.

9.2 No Delaware newborn shall be denied testing for hereditary disorders because of inability of the newborn's parents to pay the fee. A "Statement of Fee Exemption" form will be provided to the practitioner or parent requesting exemption from fees. This form must be completed and submitted to the Newborn Screening Program Office within 30 days of birth.

10.0 RELIGIOUS EXEMPTION FROM TESTING

10.1 A newborn may be excused from screening if the parent objects to the tests because the screening tests conflict with the religious tenets or practices of the parents.

TITLE 16 DELAWARE ADMINISTRATIVE CODE

10.2 In the event a religious exemption is claimed from the requirements for testing for Hereditary Disorders, the person otherwise responsible for submitting the specimen for testing shall be responsible for submitting a completed affidavit to the Delaware Newborn Screening Program Office, signed by the infant's parents, using the following language:

- 1. (I) (We) (am) (are) the (parent(s)) (legal guardian (s)) of _____ (name of child)
- 2. (I) (We) hereby (swear) (affirm) that (I) (we) subscribe to a belief in a relation to a Supreme Being involving duties superior to those arising from any human relation.
- 3. (I) (We) further (swear) (affirm) that our belief is sincere and meaningful and occupies a place in (my) (our) life parallel to that filled by the orthodox belief in God.
- 4. This belief is not a political, sociological or philosophical view of a merely personal moral code.
- 5. This belief causes (me) (us) to request an exemption from the requirements for testing for Hereditary Disorders by the Delaware Newborn Screening Program for _____ (name of child).

Signature of Parent (s) or
Legal Guardian(s)

SWORN TO AND SUBSCRIBED before me, a registered Notary Public, this _____ day of _____, 200_____.

(Seal)
Notary Public

My Commission Expires:

10.3 The Newborn Screening Refusal Form will be provided through the Newborn Screening Program Office.

11.0 PENALTY FOR NON-COMPLIANCE

Under the Authority granted to the Department of Health and Social Services, Division of Public Health under 16 Del. C. sec. 107, "whoever refuses, fails or neglects to perform the duties required under this chapter, or violates, neglects or fails to comply with the duly adopted regulations or orders of the Division shall be fined not less than \$100 and not more than \$1,000, together with costs, unless otherwise provided by law."



APPENDIX B

**Serving the Family From Birth to the Medical Home:
A report from the Newborn Screening Task Force,
American Academy of Pediatrics Publication,
August 2000, Volume 106, Number 2**

PEDIATRICS

August 2000

Volume 106

Number 2

Part 2 of 3

American Academy of Pediatrics



S U P P L E M E N T T O P E D I A T R I C S

Serving the Family From Birth to the Medical Home

*A Report From the Newborn Screening Task Force
Convened in Washington DC, May 10–11, 1999*

Sponsoring Organizations:

*Health Resources and Services Administration
American Academy of Pediatrics*

Co-Sponsoring Organizations:

*Agency for Healthcare Research and Quality
Association of Maternal and Child Health Programs
Association of Public Health Laboratories
Association of State and Territorial Health Officials
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Statements and opinions expressed in this supplement are those of the authors and not necessarily those of the American Academy of Pediatrics, its committees, or the Editor or Editorial Board of *Pediatrics*, or sponsoring institutions.

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PREFACE

Each year the 4 million infants born in the United States are screened shortly after birth to detect a variety of congenital conditions. These public health screening programs have become models for population-based screening. Newborn screening programs in this country began with the work of Dr Robert Guthrie in the 1960s with the development of a screening test for phenylketonuria (PKU). Today, all states screen for a wide range of conditions. However, the array of screening tests performed by each state varies and changes periodically. The variability reflects differences in community values, in state political and economic environments, and in technical capabilities.

The Health Resources and Services Administration's (HRSA) Maternal and Child Health programs have supported the development of these programs from their inception. HRSA funded the early work of Dr Guthrie to develop the screening test for PKU, sponsored cost-effectiveness studies for the PKU screening test, and facilitated the expansion of newborn screening programs to include screening tests for sickle cell anemia. In recognition of this historical involvement with state newborn screening programs, HRSA requested the American Academy of Pediatrics (AAP) to convene The Task Force on Newborn Screening. Genuine concern for the health of infants and children demands a periodic assessment of health service programs such as newborn screening so that these programs can provide better service. The Task Force on Newborn Screening addresses this responsibility in a thoughtful and comprehensive manner. The charge to the Task Force was to review and evaluate the issues and challenges facing the nation's newborn screening programs and to make recommendations to strengthen these programs. This Task Force has appropriately involved many groups and individuals from within and outside the newborn screening, pediatrics, and genetics communities, representing a diversity of views and expertise.

The Task Force recommendations were developed with recognition that the environmental context within which these programs were established has changed dramatically over the past 10 years. The growing impact of consumer advocacy has resulted in a congressional directive to federal agencies to expand and evaluate newborn screening programs. New technologies such as tandem mass spectrometry and DNA-based tests offer the possibility for screening for additional conditions. Changing demographics emphasize the importance of understanding the cultural uniqueness in approaches to health. The Human Genome Project provides the basis for understanding variations in risk among individuals for medically important and genetically complex human diseases. This project brings new understandings about race and ethnicity. The advances in basic and clinical science and technology resulting from the Human Genome Project will offer unparalleled promise to improve abilities to promote health and prevent, diagnose, and treat diseases in children. Not to be forgotten will be those essential ethical, legal, and social questions that must be addressed as well as the challenge in balancing the need to both protect a population's health and to respect individual rights. Further, with the advent of new technologies and new knowledge, it is critical that the newborn screening programs continue to operate under sound public health principles and are connected to medical homes to provide care that is accessible, family-centered, continuous, comprehensive, coordinated, compassionate, and culturally competent.

The task of proposing changes to meet the challenges of the 21st century, while preserving the accomplishments of the past, has been undertaken with objectivity, sensitivity, and creativity by the newborn screening, pediatric, and genetics communities. One outcome of this process is the report published here. It will provide a basis for constructive dialogue and for setting a national agenda for progress.

The HRSA wishes to thank the Task Force and members of the workgroups for their hard work and their commitment to this process. We also wish to recognize the leadership that the AAP brought to the success of this process. Finally, we would like to acknowledge Linda L. McCabe, PhD, for her skillful editing of this report.

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Serving the Family From Birth to the Medical Home

Newborn Screening: A Blueprint for the Future

Executive Summary: Newborn Screening Task Force Report

Approximately 4 million infants are born yearly in the United States (US), and are screened to detect conditions that threaten their life and long-term health. Newborn screening is a public health activity aimed at the early identification of infants who are affected by certain genetic/metabolic/infectious conditions. Early identification of these conditions is particularly crucial, as timely intervention can lead to a significant reduction of morbidity, mortality, and associated disabilities in affected infants.

Newborn screening has been universally accepted for the past 3 decades. It represented the first population-based genetic screening program, and signaled the integration of genetic testing into public health programs. Today, advances in technology are making possible new forms of newborn screening programs, such as newborn hearing screening. These technological advances will continue to have a significant impact on the sensitivity, specificity, and scope of newborn screening programs, including newborn heelstick screening.

Challenges are anticipated with technological advances. It is likely that public pressure to deploy new diagnostic capabilities, such as DNA-based technology, will increase despite limited knowledge of potential risks and benefits. In addition, the ability to detect individuals with conditions for which there is no effective or necessary treatment is likely. Further, as the Human Genome Project is completed, the impetus and opportunity for the transition of genetic technology into practice will increase. These and other challenges will affect not only newborn screening tests, but also the entire newborn screening system, which includes short-term follow-up, diagnosis, treatment/management, and evaluation. Inherent to each of these components is an education process. A national dialogue and process is needed to support state newborn screening systems as they try to keep pace with new technology.

To address these and other issues, a national Task Force on Newborn Screening (Task Force) was convened by the American Academy of Pediatrics (AAP) with funding from and at the request of the Maternal and Child Health Bureau (MCHB), Health Resources and Services Administration (HRSA), US Department of Health and Human Services (HHS). The AAP was asked to convene the Task Force in recognition that pediatricians and other primary care health professionals must take a lead in partnering with public health organizations to examine the many issues that have arisen around the state newborn screening programs.

To ensure that children who are screened are linked to a medical home, it was essential that pediatricians and other primary care health professionals be involved. The AAP defines the medical home as care that is accessible, family-centered, continuous, comprehensive, coordinated, compassionate, and culturally competent. A child who has a medical home has a pediatrician or other primary care health professional who is working in partnership with the child's family to ensure that all medical, nonmedical, psychosocial, and educational needs of the child and family are met in the local community.

Task Force members were appointed to represent many perspectives among those who operate programs, conduct research, and are affected by newborn screening systems. The co-sponsors of this effort were: other HHS agencies including the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and the Agency for Healthcare Research and Quality (AHRQ); the Genetic Alliance, which is a consortium of consumer groups; and national public health organizations including the Association of State and Territorial Health Officials, the Association of Maternal and Child Health Programs, and the Association of Public Health Laboratories. This report has been approved by the AAP Board of Directors. It does not necessarily reflect the viewpoints of sponsoring organizations or the organizations represented by members of the Task Force.

The purpose of the Task Force was to review issues and challenges for state newborn screening systems. The review process was structured to further expand representation. Task Force members were divided into 5 work groups, and additional individuals were invited to participate in each work group's examination of key issues. Over the course of 6 months, questions, concerns, and issues were collected from state public health agencies, state public health laboratory directors, maternal and child health programs, pediatricians, and other primary care health professionals who care for children, families and other consumers, bioethicists, scientists, and health services researchers. Each work group formulated conclusions and developed consensus recommendations. On May 10–11, 1999, the Task Force heard presentations from the 5 work groups, along with public comment on the reports and recommendations. A set of recommendations was developed incorporating key elements of the work group reports, issues raised by the public, and other related information. This document summarizes the Task Force recommendations.

The Task Force has outlined a national agenda for strengthening each "state" newborn screening system. ("State" newborn screening systems refer to state and territorial programs for heelstick newborn screening.) The Task Force believes that public health agencies (federal and state), in partnership with health professionals and consumers, should continue to:

- Better define public health responsibilities for federal and state public health agencies;
- Develop and disseminate model state regulations to guide implementation of state newborn screening systems (including disease and test selection criteria);
- Develop and evaluate innovative testing technologies;
- Design and apply minimum standards for newborn screening activities (eg, sample collection, laboratory quality, sample storage, and information systems);
- Develop and disseminate model follow-up, diagnosis, and treatment guidelines and protocols for health professionals, and other participants in the newborn screening system;
- Design and evaluate model systems of care with services and supports from infancy to adulthood that are consistent with national guidelines for children with special health care needs (ie, family-centered, community-based, and coordinated systems of care).
- Design and evaluate tools and strategies to inform families and the general public more effectively; and
- Fund demonstration projects to evaluate technology, quality assurance, and health outcomes.

KEY RECOMMENDATIONS

I. Effective Newborn Screening Systems Require an Adequate Public Health Infrastructure and Must Be Integrated With the Health Care Delivery System

- Federal agencies must take action to strengthen the public health infrastructure for newborn screening.
 - The federal government—acting through the HRSA, CDC, Health Care Financing Agency (HCFA), AHRQ, NIH, and other agencies—should collaborate to provide ongoing leadership and support for development of newborn screening standards, guidelines, and policies.
 - As the federal unit with most responsibility for newborn screening system development, the HRSA should engage in a national process involving government, professionals, and consumers to advance the recommendations of this Task

- Force and assist in the development and implementation of nationally recognized newborn screening system standards and policies.
- Federal resources should be identified to sustain a Newborn Screening Quality Assurance Program to assist state public health laboratories. Such assistance must be both sustained and expanded as states adopt new screening technologies and modalities.
- The HRSA's MCHB should strengthen current mechanisms to improve coordination of infant health programs and initiatives within the state and/or between states, including continuation of funding in support of newborn screening program reviews.
- State public health agencies should direct their newborn screening program to be consistent with professional guidelines and recommendations. Each state public health agency should take responsibility for systems development. Specifically, states and their agencies have responsibility to:
 - Design and coordinate the newborn screening system;
 - Adhere to nationally recognized recommendations and standards for the validity and utility of tests. State newborn screening systems have a responsibility to review the appropriateness of existing tests, tests for additional conditions, and new screening technology and modalities; and
 - Adopt standards for laboratories, health professionals, and health care financing plans based on nationally recognized standards and guidelines for follow-up, diagnosis, and treatment.
- State public health agencies, working under legislative authority, have the ongoing responsibility to ensure quality and evaluate program effort. States and their state public health agencies should:
 - Maintain a newborn screening system that has appropriate evaluation, performance monitoring, and quality assurance activities from initial screening, through follow-up, diagnosis, treatment, and services through adolescence and adulthood;
 - Conduct oversight of program operations, including those outside the public health agency, such as test analysis and tracking, private sector collection and transmission of screening data, laboratory quality, and the quality of the diagnostic procedures and treatment programs at pediatric subspecialty clinics; and
 - Monitor and evaluate program performance through collection, assembly, analysis, and reporting of data, including outcome evaluations.
- States and state public health agencies should implement mechanisms to inform and involve health professionals and the public. Each state should:
 - Develop a program advisory board that is multidisciplinary, involves pediatricians and other primary care health professionals who provide medical homes for children, pediatric subspecialists, and has meaningful representation of families and the general public; and
 - Design and implement public, professional, and parent education efforts regarding newborn screening.
- States and state public health agencies should provide support for coordination and integration of program activities, including information and services. This will require public—private, federal—state, and intrastate partnerships. States should:
 - Use public and private resources to fund demonstration programs that can serve as a testing ground for linking information and services in ways that improve the newborn screening system; and
 - Structure interagency coordination to maximize resources and to improve the efficiency and effectiveness of newborn screening systems.
- Ensure that all newborns admitted to their practice have received adequate newborn screening, and that appropriate documentation of testing is present;
- Follow positive screening results to diagnosis (ie, confirmed or excluded), including repeated screening and diagnostic testing;
- Coordinate a seamless system of care with pediatric subspecialty clinics, tertiary care centers, and/or community-based providers, when a child is diagnosed with a disorder through newborn screening;
- Maintain a central record and database containing all pertinent medical information about the child. This record should be accessible to the family and others involved in the child's care, but confidentiality must be ensured; and
- Assist the family in understanding the diagnosis, symptoms, and potential implications of a diagnosed genetic/metabolic condition, as well as the availability of genetic counseling, family testing, and other family support services.
- Parents should receive information (on behalf of their children) about newborn screening.
 - Prospective parents should receive information about newborn screening during the prenatal period. Pregnant women should be made aware of the process and benefits of newborn screening and their right of refusal before testing, preferably during a routine third trimester prenatal care visit.
 - Parent knowledge should be reinforced after delivery by educational materials and discussion as needed by the infant's pediatrician or primary care health professional and/or knowledgeable hospital staff.
 - Prenatal health care professionals as well as the infant's primary care health professional should be knowledgeable about their state's newborn screening program through educational efforts coordinated by the state's newborn screening program in conjunction with a newborn screening advisory body.
- Written documentation of consent is not required for the majority of newborn screening tests, for example, those tests of proven validity and utility.
 - Parents should always be informed of testing and have the opportunity to refuse testing.
 - If after discussions about newborn screening with health professionals, parents refuse to have their newborn tested, this refusal should be documented in writing and honored.
 - If a newborn screening test is investigational or in the process of being developed, the benefits or potential risks have yet to be demonstrated, and identifiers are not removed from the specimen, informed consent should be obtained from parents and documented.
- Studies should be performed to broaden understanding of the ways in which communication can be performed more effectively for the benefit of consumers.
 - Pilot studies and evaluation research should be conducted to assess the potential impact of revised parental permission and informed decision-making policies.
 - Each state or region should, with input from families who have children with special needs and/or parent information centers, develop and provide family educational materials about newborn screening.
 - Evaluation of materials should be ongoing, particularly because of the changing demographics of childbearing, cultural changes, and rapid developments in genetic science.
- Parents have a right to confidentiality and privacy protections for the medical and genetic information in any type of newborn screening results. Based on nationally recognized standards and guidelines, each state should have appropriate policies and mechanisms in place to ensure families' privacy and confidentiality. Laws to guarantee genetic privacy and protect against genetic discrimination should benefit patients identified by newborn screening.
- States and the federal government should include public participation in medical policy-making. The Secretary's Advisory Committee on Genetic Testing provides a mechanism for public participation in genetic policy development at the federal level. Each state should establish and fund a newborn screening advisory body with public participation to advise on newborn screening policy developments.
 - Such an entity should include a broad range of public advisors representing parents, health professionals, third-party

II. Public Health Agencies Must Involve Health Professionals, Families, and the General Public in the Development, Operation, and Oversight of Newborn Screening Systems

- The pediatrician or primary care health professional who, in partnership with parents, is the source of the child's medical home, should:

- payers, appropriate government agencies, and other concerned citizens.
- Such an entity should be empowered to advise state officials about screening for particular conditions based on accepted standards and be consulted about the development of related state regulations.
 - Such an entity should be involved in the review of new tests under consideration by the state and in the development of pilot programs for new tests.
 - Such an entity should be involved in the ongoing evaluation of all aspects of the state's process for newborn screening. Oversight activities should include a review of: testing, follow-up, and treatment efforts; the impact on families of receiving a false-positive screening result; and the state's process for handling consumer input including grievances.

III. Public Health Agencies Must Ensure Adequate Infrastructure and Policies for Surveillance and Research Related to Newborn Screening

- State Maternal and Child Health (MCH) programs should conduct a review of the newborn screening system and its relationship to the HRSA MCH Block Grant Performance Measures and evaluate the quality of data of the newborn screening-related performance measures.
- The federal HCFA should develop Health Plan Employer Data and Information Set (HEDIS) measures to evaluate the health plans' performance within the newborn screening system.
- A federally-funded newborn screening research agenda should be outlined that aims to: develop better tests (more sensitive, more specific, and less costly); assess the validity and utility of new technologies (eg, tandem mass spectrometry, DNA-based testing, and other evolving technologies); and define appropriate uses of residual biologic samples for population-based research and surveillance.
- The HRSA's MCHB should provide grants to states to stimulate development of newborn screening information systems, with a focus on newborn screening systems that are connected to the medical home, newborn screening system process and outcome evaluation, development of standardized data sets, analyses of cost-efficiency and effectiveness, and integration with other public health data systems. Support for technological innovation (ie, new test technologies) should include these measures.
- Pediatricians, pediatric subspecialists, and other health professionals who care for children should contribute to newborn screening data collection to advance knowledge about health outcomes and intervention effectiveness. Professional associations, the HRSA-funded National Newborn Screening and Genetics Resource Center, and state newborn screening programs should develop strategies to assist health professionals in their efforts to participate in and learn from newborn screening information systems.
- Pilot studies should be undertaken to demonstrate the safety, effectiveness, validity, and clinical utility of tests for additional conditions and new testing modalities. Informed consent of parents is called for in all such pilot studies. These studies might be undertaken by individual states, regional or nationwide groups of states, or through federal grants provided to research institutions across the country.
- Federal and state public health agencies, in partnership with health professionals, families, and representatives of ethnic, minority, and other diverse communities should:
 - Develop model legislation and/or regulation that articulates policies and procedures regarding utilization of unlinked and identifiable residual samples for research and public health surveillance. This process should include review and consideration of the recent recommendations to the President set forth by the National Bioethics Advisory Commission (NBAC) for research involving human biological materials;
 - Develop model consent forms and informational materials for parental permission for retention and use of newborn screening samples;

- Develop educational materials for parents that includes information regarding the storage and uses of residual samples;
- Organize collaborative efforts to develop minimum standards for storage and database technology to facilitate appropriate storage of residual newborn screening blood samples at the state level; and
- Consider creating a national or multi-state population-based specimen resource for research in which consent is obtained from the individuals from whom the tissue is obtained. Such a resource could be an alternative to retaining newborn screening samples for potential use in research.
- Using national recommendations, each State program should develop and implement policies and procedures for retention of residual newborn screening blood samples that articulate the rationale and objectives for storage, the intended duration of storage, whether storage is with or without identifiers, and guidelines for use of identifiable and unlinked samples. An advisory group for newborn screening programs with broad health professional and family/community representation is a valuable resource in developing policies and procedures and in reviewing applications for use of retained samples. The advisory body also could determine priorities for use.

IV. Public Health Agencies Should Ensure Adequate Financing Mechanisms to Support a Newborn Screening Program

- States should ensure adequate financing, of all parts of the newborn screening system: screening, short-term follow-up, diagnostic testing, comprehensive medical care/treatment, and evaluation of the system. If newborn screening fees are not adequate, funding of all components of the system could be accomplished with other public health dollars or by third-party payers. Other uses of newborn screening fees should not be considered until all of the components of the newborn screening system are fully funded.
- States should take responsibility for blending resources available through Title XIX (Medicaid), Title V (MCH Block Grant), Title XXI (State Children's Health Insurance Program) [SCHIP], and private insurance to guarantee necessary coverage and financing for all children and adolescents with a condition diagnosed through the newborn screening system.
- State contracts for publicly-subsidized third-party insurance plans that cover children (eg, Medicaid and SCHIP) should explicitly require coverage for newborn screening and those services and treatment related to disorders identified by newborn screening. State contracts also should require that third-party payers ensure access to health care professionals with appropriate pediatric expertise within the network or through out-of-network referrals.
- States, in cooperation with health professionals and payers, should put mechanisms in place to identify the third-party payers for newborns immediately following birth. For example, all states should operationalize the automatic newborn eligibility requirements under Medicaid and the Health Insurance Portability and Accountability Act (HIPAA) newborn coverage provisions that require infant coverage and prohibit preexisting condition exclusions for newborns.
- Purchasers—public and private—should ensure that the benefits package they pay for includes the care and services defined by the AAP Scope of Health Care Benefits Statement and the Council of Regional Networks for Genetic Services Guidelines.
- In the Supplemental Security Income (SSI) program, the federal government should review the technical appropriateness of guidelines, and evaluate the consistency of their application, for children with conditions identified through newborn screening.

Serving the Family From Birth to the Medical Home

Newborn Screening: A Blueprint for the Future

A Call for a National Agenda on State Newborn Screening Programs

ABBREVIATIONS. PKU, phenylketonuria; AAP, American Academy of Pediatrics; MCHB, Maternal and Child Health Bureau; ARC, Association for Retarded Citizens; MCH, maternal and child health (programs); CDC, Centers for Disease Control and Prevention; HRSA, Health Resources and Services Administration; CSHCN, Children With Special Health Care Needs; CORN, Council of Regional Networks for Genetic Services; NAS, National Academy of Sciences; IOM, Institute of Medicine; HHS, US Department of Health and Human Services; NIH, National Institutes of Health; AHRQ, Agency for Healthcare Research and Quality; APHL, Association of Public Health Laboratories; SACGT, Secretary's Advisory Committee on Genetic Testing; CLIA, Clinical Laboratory Improvement Amendments; HCFA, Health Care Financing Administration; NSQAP, Newborn Screening Quality Assurance Program; WIC, Supplemental Nutrition Program for Women, Infants, and Children; HEDIS, Health Plan Employer Data and Information Set; NBAC, National Bioethics Advisory Commission; IRB, institutional review board; OTA, US Congress Office of Technology Assessment; SSI, Supplemental Security Income; SCHIP, State Children's Health Insurance Program; HIPAA, Health Insurance Portability and Accountability Act; ERISA, Employee Retirement and Income Security Act; EPSDT, Early and Periodic Screening, Diagnosis, and Treatment (program).

I. BACKGROUND

Newborn screening in the United States is a public health program aimed at the early identification of conditions for which early and timely interventions can lead to the elimination or reduction of associated mortality, morbidity, and disabilities. This screening takes place within the context of a newborn screening system, and involves the following components: screening, short-term follow-up, diagnosis, treatment/management, and evaluation. Inherent to each of these components is an education process.

The screening programs like these for the 4 million infants born each year in the United States have been heralded as successful and cost-effective.¹⁻⁵ The newborn screening program's efficiency and effectiveness depends on the smooth integration of sample collection, laboratory testing, follow-up, diagno-

sis, timely treatment, and tracking of outcomes.⁶⁻¹¹ The foundation and justification of newborn screening systems rest on the principles that testing procedures are readily available; technically feasible; economically sound; and clearly beneficial to affected newborns, their families, and to society.^{10,12-14} The universal acceptance of newborn screening for specified conditions over the past 3 decades attests to the undeniable benefits that flow from early testing and prompt, appropriate therapy. However, although newborn screening systems have succeeded in preventing morbidity and mortality, controversies, challenges, and opportunities continue.

The History of Newborn Screening

Newborn screening programs began in the early 1960s with the original work of Dr Robert Guthrie, who developed a screening test for phenylketonuria (PKU) and a system for collection and transportation of blood samples on filter paper.^{15,16} By 1962, Massachusetts launched a voluntary newborn PKU screening program that demonstrated the feasibility of mass genetic screening.¹⁷

Initially, newborn screening for PKU was not a health department role or a legislated activity. Health professionals were slow to adopt the practice of screening for PKU, and the responsibility for screening was not defined (eg, should it be the responsibility of the hospital in which the infant was born, the mother's obstetrician, or the infant's pediatrician or primary care health professional). The American Academy of Pediatrics (AAP), acting as the professional association that develops policy for the care of children, raised concerns about the sensitivity and specificity of PKU screening tests, as well as the efficacy of early intervention for PKU.^{16,17} Out of these concerns, the need for further research about this testing was recognized, and the federal Children's Bureau (now the federal Maternal and Child Health Bureau [MCHB]) funded a collaborative study to address questions and concerns about the effectiveness of the PKU screening test.^{16,17}

At the same time, advocates for children remained concerned that children with undetected PKU were at high risk for mental retardation.^{16,17} The National Association for Retarded Citizens (now the ARC)

From the AAP Newborn Screening Task Force, Elk Grove Village, Illinois. Received for publication Mar 13, 2000; accepted Mar 14, 2000.

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proposed model legislation for creation of public programs to address low detection rates, and also conducted an extensive grass-roots lobbying effort to support passage of mandatory PKU screening legislation.¹⁶ Many state health departments supported the adoption of such legislation. The Kennedy Administration, with the guidance of the Presidential Advisory Commission on Mental Retardation, was also supportive. The Commission hired the Advertising Council, which mounted a public campaign for mandatory PKU screening. Other advocacy groups, such as the March of Dimes Birth Defects Foundation, mobilized volunteers to lobby for passage of legislation at the state level. As a result of this multidimensional advocacy campaign, most states passed laws in the early 1960s that mandated newborn screening for PKU.¹⁷⁻¹⁹ Forty-three states had formal statutes by 1973. State health departments, particularly their maternal and child health (MCH) programs (funded by Title V of the Social Security Act of 1935), assumed the central role in implementation of these new laws.^{16,17}

As a response to this mandate, some states set up screening laboratories or added phenylalanine analysis to their state laboratory's repertoire of tests. In other states, private laboratories played a major role. Quality control was difficult because of the number of and the variability among testing sites; and became even more difficult as states added other genetic tests to their newborn screening batteries. Early in the 1970s, the need to improve quality assurance through systematic proficiency testing was recognized. In an early proficiency-testing study, the Centers for Disease Control and Prevention (CDC) found marked variability among health department laboratories. As a result, the Newborn Screening Quality Assurance Program was begun at the CDC, with additional funding from the Health Resources and Services Administration (HRSA).²⁰ (See further discussion in Section II, Public Health Infrastructure.)

In 1976, federal legislation to support screening for genetic diseases was adopted, and in fiscal years 1979 and 1980, 34 state genetic service programs received federal funding.^{21,22} This support was welcomed by the states, as the cost of screening tests and the health departments' coordination of screening activities had not been completely covered by many state budgets.

As a result of the laws mandating PKU testing, and the establishment of health department newborn screening units that occurred in the 1960s and 1970s:

- Every newborn had an opportunity to be screened for PKU when laws were properly implemented; consequently, most were screened.
- Financial barriers to screening and diagnosis were removed, but families often had to pay for the special formula, special foods, and other related treatments.
- State newborn screening programs evolved, with the goal of providing safe screening tests and appropriate follow-up to every newborn.¹⁷

During the 1980s, further systems development took place at the state and regional level. Newborn

screening systems were set up by public health agencies to ensure coordination between the hospitals from which most specimens were received, the public health laboratory, the infant's pediatrician or primary care health professional to whom positive results were reported, and pediatric subspecialists to whom infants were referred for diagnosis and treatment.^{7,12,23-26} Together these entities comprised the backbone of newborn screening systems. Some state newborn screening systems also played a role coordinating follow-up^{25,27}; depending on their public health structure, medical care structure, and available resources. In many states, the Title V Children With Special Health Care Needs (CSHCN) programs performed this role.

In 1985, the Council of Regional Networks for Genetic Services (CORN) was developed in response to the need for an organization to facilitate state genetic program efforts through coordination and special initiatives. The CORN published newborn screening system guidelines that defined a 5-part system of screening, follow-up, diagnosis, treatment/management, and evaluation.^{7,9} These guidelines were not treatment guidelines or standards of care, but provided public health agencies with a detailed framework for a systems approach to newborn screening.

By 1985, 12 states had laws allowing charges or fees for screening tests.¹⁸ Today, a majority of the states have established newborn screening fees to be collected from the health care professional, birthing facility, third-party payer, or the parent of the newborn (see Section V, The Economics of Screening). Although newborn screening fees are collected in most states, financing the treatment of children identified with genetic conditions through newborn screening remains problematic. Eligible families in many states are ensured access to therapy (eg, low phenylalanine diet for PKU),^{15,16} particularly when the special formula is deemed a prescription drug. Families deemed ineligible financially may be burdened by the cost of necessary treatments. However, when special PKU formula is classified as a food, many health insurers refuse to cover it at all; creating a problem for both eligible and ineligible families.

Now, after >30 years of experience with PKU, it is clear that knowledge regarding PKU and the approach to newborn screening were rudimentary when the programs were first launched. Studies to validate the screening test, and to assess the safety and effectiveness of a special diet to prevent mental retardation, were completed after laws were implemented. However, the history of these efforts has set the context for the role of public health in newborn screening and genetics.

Setting the Framework for State Newborn Screening Systems

Guidance for newborn screening systems have been in place for 2 decades. These guidelines are inextricably linked to ethical, legal, and social considerations and based on the premise that screening should be conducted only when science and technology can serve both the individual and public good.

Three landmark reports emphasize the criteria that should be used to justify population-based newborn screening systems, and include: the National Academy of Sciences' (NAS) *Genetic Screening: Programs, Principles, and Research* in 1975²⁰; the Institute of Medicine (IOM) report, *Assessing Genetic Risks: Implications for Health and Social Policy* in 1994²⁸; and *Promoting Safe and Effective Genetic Testing in the United States: Final Report of the Task Force on Genetic Testing*, in 1997.²⁹

The NAS Report

The 1975 NAS report set forth rigorous guidelines about the criteria for newborn screening including: evidence of substantial public benefit and acceptance (including acceptance by health care professionals); previous feasibility study; satisfactory test methods; appropriate laboratory facilities and quality control; resources for counseling, treatment, and follow-up; acceptable costs; effective education; informed consent; and the means to evaluate the effectiveness and success of each step. The National Research Council raised concerns about what it saw as the potential risks of inappropriate newborn screening. The NAS report was critical of how PKU screening had developed and suggested the establishment of patient advisory committees made up of individuals with medical and nonmedical expertise.²⁰

The IOM Report

The 1994 IOM Committee on Assessing Genetic Risks recommended that:

"Newborn screening only take place 1) for conditions for which there are indications of clear benefit to the newborn, 2) when a system is in place for confirmatory diagnosis, and 3) when treatment and follow-up are available for affected newborns. . .

The Committee believes that mandatory offering of established tests (eg, PKU, congenital hypothyroidism) that lead to the diagnosis of a treatable condition, is appropriate. If there is no other way to ensure that affected newborns will be identified and have access to effective treatment (eg, in PKU, congenital hypothyroidism), then mandatory newborn screening is acceptable. . .

*Mandatory newborn screening should only be undertaken if there is strong evidence of benefit to the newborn from effective treatment at the earliest possible age (eg, PKU and congenital hypothyroidism)."*²⁸

Although the Committee did point to the appropriateness of the "mandatory offering" of newborn screening tests, they emphasized the use of the informed consent process to educate parents. The IOM report also pointed out that even in cases where a treatment is available for a disorder detectable through newborn screening, timing may or may not be crucial; that is, it may provide no greater or lesser benefit if started after symptoms appear. For example, treatment of children identified through screening for maple syrup urine disease may have only limited effectiveness at best, and parents may face a quandary about whether or not to treat. Even if hypothetical benefits exist, newborn screening systems need close scrutiny to determine if the necessary treatments are actually provided to the children. In states that support screening but not treatment, families may be unable to afford treatment and thus, children may not benefit from screening. For exam-

ple, many children with sickle cell anemia do not get their necessary penicillin prophylaxis and comprehensive medical care. Also, parents of children with PKU are given educational information about diet and nutrition in most states, but not all states provide funds for the expensive essential diet or other food assistance.⁶

The Final Report of the Task Force on Genetic Testing

The 1997 report entitled *Promoting Safe and Effective Genetic Testing in the United States: Final Report of the Task Force on Genetic Testing* pointed out that newborn screening should be of primary benefit to the infant identified. Like the IOM report, the Task Force on Genetic Testing report stated that it would be inappropriate to use traditional newborn screening solely to determine the carrier status of the infant. Moreover, the test should have analytical and clinical validity and utility. Interventions to improve the outcomes for an infant must be safe and effective.

The Final Report of the Task Force on Genetic Testing differed from the IOM Report in that, the Task Force felt that informed consent for newborn screening could be waived, provided that "the analytical and clinical validity and utility of the test" had been established. If the validity and utility of the tests were not established, then informed consent would be required.²⁹

New Challenges Facing Today's State Newborn Screening Systems

As a population-based public health activity, newborn screening systems are housed in state public health agencies. They operate under policies determined at the state level, and ideally, within the framework of the public health core functions of assessment, assurance, and policy development. States vary in public health infrastructure, newborn screening policy establishment, laboratory capacity, screening techniques, as well as in the laws that define the scope of services mandated in response to the identification of a condition. State newborn screening systems also vary in available system components, and in financing mechanisms to pay for these components.

Notably, the array of screening tests performed by each state varies and changes periodically. All state programs now include screening tests for PKU and congenital hypothyroidism. More than 40 programs screen for sickle cell disease and 48 screen for galactosemia. Some newborn screening systems include tests for congenital adrenal hyperplasia, homocystinuria, maple syrup urine disease, and biotinidase deficiency^{6,30} (see Fig 1 and Table 1). A few states also include screening tests for cystic fibrosis, tyrosinemia, additional metabolic conditions, and/or other conditions such as congenital infections (ie, HIV). Over half of the states now require all newborns be screened for hearing loss.³¹⁻³³

The mechanism for deciding which screening tests to include as part of a population-based newborn screening system varies among programs. Thus, the disorders screened for vary from state to state.^{6,18,35-37} These inconsistencies reflect differences

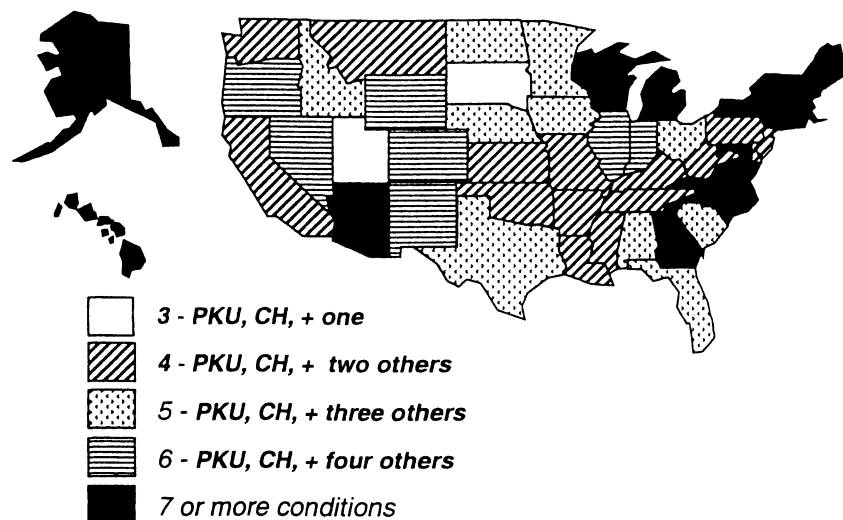


Fig 1. Conditions included in state newborn screening programs, 2000.

in community values, in state political and economic environments, and in public health technical capabilities. Inequities regarding the selection of disorders for newborn screening panels are illustrated by sickle cell disease, a condition for which neonatal screening markedly reduces morbidity and mortality during early childhood. Nationally, sickle cell disease is the most prevalent condition included in newborn screening programs; however, disease prevalence within states varies more than 50-fold because of the widely differing ethnic populations of states. Currently, 41 states and the District of Columbia conduct universal screening for sickle cell disease. Three states conduct screening in infants of high-risk ethnic groups, and 6 states conduct no routine screening. These 9 states are among those with the lowest prevalence of sickle cell disease. Concerns about prevalence, cost-effectiveness, as well as concerns about the acceptability of screening to health professionals and the general public, have hindered implementation of this test despite an NIH-consensus conference recommendation for universal screening.^{3,38-41} In some cases, misperceptions about the benefits of screening, misperceptions about the prevalence of the disease in various ethnic groups, and/or the lack of effective advocacy for the disease have also contributed.⁴²⁻⁴⁵ Thus, while an African-American infant born in a state that does not universally screen for sickle cell disease has the same risk for sickle cell disease as an African-American infant born in a state with universal screening for sickle cell disease, the infant born in the non-screening state is denied the important benefit of screening. In this regard, it is interesting to note that the relatively low prevalence of sickle cell disease in each of the 9 states without universal screening for the disorder (estimated to be >1:40 000) is still higher than the prevalence of galactosemia (estimated to be about 1:60 000-80 000), a disorder included in the screening panels of all 9 states.^{30,46-48} This situation highlights the need for a more uniform national policy for the selection of newborn screening tests.⁴⁹

Because advances in science and technology are

continually making it possible to screen for additional conditions, the decision about which tests to include in a newborn screening panel are complex.⁵⁰⁻⁵⁴ Moreover, in an era of accountability, decision-making is hampered by the lack of studies of and data about test validity and health outcomes. With existing variations between state newborn screening systems, a national model of the structure and function of newborn screening systems has not yet been embraced. Furthermore, there are no uniform guidelines for the periodic assessment of conditions for which screening is performed.^{7,9} As a result, infants across the country do not have equal access to newborn screening and its potential to prevent morbidity and mortality. The US Surgeon General, Dr David Satcher, has emphasized the need for the nation to address unequal access to health care, and the health disparities created by these inequalities. National standards are needed to promote greater comparability of newborn screening programs and address such inequities.⁵⁵

The work of David Hall and his colleagues in the United Kingdom provides useful guidance about creating equitable, sustainable, and effective newborn screening programs.^{56,57} Speaking in Washington, DC, on May 10, 1999, Dr Hall reminded the Task Force of the responsibility to do more than provide screening tests, saying: "If it is important enough to screen for, it is important enough to follow-up." He also spoke on the issues of quality assurance and adequate funding for newborn screening systems stating, "The balance is fine between good and harm in screening. Unless a screening program is a good one, it can do more harm than good."

In the United States, technological advances have had, and will continue to have a significant impact on the sensitivity, specificity, and scope of newborn screening. Pressure is mounting to deploy new diagnostic capabilities despite possessing limited knowledge of their risk and benefit, or their analytical or clinical validity and utility. Presently, tandem mass spectrometry offers, and shortly, DNA-based technology will offer the possibility of using one test or

Table 1. U.S. National Screening Status Report, July 2000

The National Screening Status Report lists the status of newborn screening in the United States. All infants in a state must be screened in order for a dot to be added.

	Phenylketonuria	Congenital Hypothyroidism	Galactosemia	Maple Syrup Urine Disease	Homocystinuria	Biotinidase	Sickle Cell Disease	Congenital Adrenal Hyperplasia	Other
Alabama	
Alaska	a	.	
Arizona	a	
Arkansas		6
California		6
Colorado	a	2, 6
Connecticut	2a, 6
Delaware		
D.C.		7
Florida	6
Georgia	3
Hawaii	6
Idaho			
Illinois	6
Indiana	6
Iowa	
Kansas		6
Kentucky		6
Louisiana	6
Maine	a	.	5, 6
Maryland	3, 6
Massachusetts	1,2a,5, 6
Michigan	
Minnesota	
Mississippi		6
Missouri		6
Montana	.	.	.				a		2a
Nebraska	6
Nevada		
New Hampshire		a		1, 6
New Jersey		
New Mexico	
New York		4, 6
North Carolina	5
North Dakota	
Ohio		
Oklahoma		6
Oregon		6
Pennsylvania		
Rhode Island	6
South Carolina	
South Dakota	.	.	.						
Tennessee	a	
Texas	6
Utah	.	.	.						6
Vermont		
Virginia	6
Washington	
West Virginia	.	.	.				a		6
Wisconsin	.	.	.	a		.	.	.	2,5
Wyoming		2, 6

a = Selected population, pilot program, or planning underway

1 = Toxoplasmosis

2 = Cystic fibrosis

3 = Tyrosinemia

4 = HIV

5 = MCAD

6 = Mandatory universal hearing screening

7 = G6PD

simpler tests to detect a larger group of genetic conditions.⁵⁸⁻⁶¹ Furthermore, as the Human Genome Project is completed, the impetus and opportunity to translate genetic knowledge and technology into public health practice will increase.⁶² With these new

technologies comes the ability to detect individuals affected by genetic conditions for which there is no clear advantage to early testing, no early or effective treatment, or no available treatment.⁶³ How should we best use these emerging diagnostic capabilities in

our newborn screening systems and, more generally, in improving the health outcomes of our children?

An updated, consistent national agenda is needed to ensure that state-based newborn screening systems understand and keep pace with new technology. State policymakers and program managers cannot be expected to make optimal decisions in isolation. The process of setting a national agenda for state newborn screening systems requires the involvement of experts in science, medicine, public health, law and ethics, as well as the public and government officials from the federal, state, and local level. The process for these deliberations must take into account public concerns about privacy, confidentiality and discrimination, recent changes in the public health and health care delivery systems, the impact of new advances in science and technology, and the potential cost-effectiveness of revised policies and programs. Such a national agenda can serve as a guide for states seeking to strengthen their newborn screening systems, and provide more equitable access to this public health preventive program for our neonates.

The Task Force on Newborn Screening

To address these and other issues, a national Task Force on Newborn Screening was convened by the AAP, with funding from and at the request of the MCHB, HRSA, and the US Department of Health and Human Services (HHS). Co-sponsors of this effort were: other HHS agencies, the National Institutes of Health (NIH), the CDC, and the Agency for Healthcare Research and Quality (AHRQ); the Genetic Alliance, a consortium of consumer groups; and national public health organizations including the Association of State and Territorial Health Officials, the Association of Maternal and Child Health Programs, and the Association of Public Health Laboratories (APHL).

The AAP was asked to convene the Task Force in recognition that pediatricians and other primary care health professionals must take a lead in partnering with public health organizations to examine the many issues that have arisen around the state newborn screening programs. To ensure that children who are screened are linked to a medical home, it was essential that pediatricians and other primary care health professionals be involved. The AAP defines the medical home as care that is accessible, family-centered, continuous, comprehensive, coordinated, compassionate, and culturally competent. A child who has a medical home, has a pediatrician or other primary care health professional who is working in partnership with the child's family to ensure that all medical, nonmedical, psychosocial, and educational needs of the child and family are met in the local community.⁶⁴

Task Force members were appointed to represent many perspectives and interests among those who operate programs, conduct research, and are affected by newborn screening (See credits page). This report has been approved by the AAP Board of Directors. It does not necessarily reflect the sponsoring organizations' viewpoints, nor do the sponsoring organiza-

tions that provided support for the Task Force necessarily endorse all of the recommendations of the Task Force.

The purpose of the Task Force was to review issues and challenges for these newborn screening programs. The review process was structured to further expand representation. Task Force members were divided into 5 work groups, and additional individuals were invited to participate in each work group's examination of key issues. The work groups were:

- Newborn Screening and Its Role in Public Health,
- Medical Home and Systems of Care,
- Economics of Screening,
- Ethical, Legal, and Social Issues, and
- Implementation and Assessment Issues.

Over the course of 6 months, questions, concerns, and issues were collected from state public health agencies, state public health laboratory directors, MCH programs, pediatricians and other health professionals, families and other consumers, bioethicists, scientists, and health services researchers. Each work group formulated conclusions and developed consensus recommendations. On May 10–11, 1999, the Task Force heard presentations from the 5 work groups, along with public comment on the reports and recommendations. A set of recommendations was developed incorporating key elements of the work group reports, issues raised by the public, and other related information.

Principles and Underlying Assumptions Used to Develop the Task Force Recommendations

Through the past 37 years of experience with newborn screening in the United States and around the world, certain underlying principles and criteria have become widely accepted. The Task Force recommendations are based on the following principles and underlying assumptions.

- Infants should benefit from and be protected by newborn screening systems.
- Not all conditions are good candidates for newborn screening. The criteria for inclusion of a screening test are: a) the condition is an important health problem that occurs frequently enough to justify screening an entire population; b) the treatment for the condition is effective when initiated early, accepted among health care professionals, and available to all screened newborns; and c) the test is simple, safe, precise, validated, and acceptable.
- Newborn screening is more than testing—it should always be part of a system that includes screening tests, follow-up, diagnosis, treatment, and evaluation as necessary. The primary objective of each state's newborn screening system should be to ensure that every newborn receives appropriate and timely services.
- Newborn screening is an essential public health prevention activity that requires integration of parent education, sample collection, laboratory analysis, primary and specialty medical care, and related services for families with affected children.

- State public health agencies should assume responsibility for assessment, assurance, and policy development in the context of newborn screening, giving particular attention to the adequacy of system structures, oversight, and funding.
- The complete newborn screening system (testing, follow-up, diagnostic procedures, treatment, and evaluation) should be clinically, socially, and ethically acceptable to the public and health professionals.
- Infants should have a "medical home" (identified by parents before or after birth) that is linked to a newborn screening system and includes access to appropriate care and treatment, if a condition is diagnosed.
- Infants born anywhere in the United States should have access to screening tests and procedures that meet accepted national standards and guidelines. New screening tests should meet national criteria for newborn screening, with data on the validity of new tests and the clinical utility of screening new diseases collected through pilot programs.
- Before newborn screening, parents (on behalf of their children) have a right to be informed about screening, and have the right to refuse screening. They also have a right to confidentiality and privacy protections for information contained in all newborn screening results.
- Increased coordination and uniformity, among state newborn screening systems and other child health programs, will greatly benefit families, health care professionals, and public health agencies.
- Parents and consumers must be involved in all parts of the policy-making and implementation process.

Screening and Counseling for Genetic Conditions in 1983

The President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research made recommendations entitled "Screening and Counseling for Genetic Conditions" in 1983.¹⁶ Many of these earlier recommendations have striking resonance today, despite the advances in science, technology, and medical care. The following findings (excerpted from that report) illustrate the continuity between earlier consideration of ethical issues in screening, and the work of the Task Force on Newborn Screening. The Commission found that:

- The parties involved, including regulators, funding agency administrators, industry representatives, researchers, and public health officials, should meet to discuss their respective roles in ensuring that a prospective test is studied adequately before screening programs are introduced.
- Successful programs require concrete goals and specific procedural guidelines that are founded on sound ethical and public policy principles.
- If ethical and policy goals are to be promoted, every screening program should have an evaluation component.
- Oversight bodies can provide an important focus for the successful provision of services.

- Public screening programs should not be implemented until they have first demonstrated their value in well-conducted pilot studies.
- Cost-benefit analysis must be regarded as a technical instrument to be used within an ethical framework, rather than as a method of avoiding difficult ethical judgments.

Task Force Assumptions Regarding the Future of Newborn Screening

The value of a blueprint depends in large part on how well the architects understand the setting. Although many unforeseeable events may change the landscape, an assessment of the environment is essential. The Task Force anticipates that the following trends will affect the future of newborn screening over the next 5 to 10 years.

- The newborn screening system affects many people and institutions, which in turn creates potential for problems related to conflicts and gaps in follow-up and services. With changes in the health care delivery system, financing, medical practice, and public health agency structures, such problems are likely to increase.
- The dramatic advances in genetic science are changing the environment for newborn screening. As the Human Genome Project is completed, the expansion of genetic knowledge and technology into public health will continue, presenting opportunities for understanding and promoting better health, lowering mortality and morbidity, and preventing diseases. As the Human Genome Project reaches fruition, medical genetics and the number of genetic risk factors for diseases that can be detected will grow rapidly. New DNA-based testing technology will be one outgrowth of applied research.
- Technological advances have had and will continue to have a significant impact on the sensitivity, specificity, and scope of newborn screening. Tandem mass spectrometry offers the possibility of detecting a larger group of metabolic conditions. With this new technology comes the ability to detect individuals with metabolic conditions for which there are no effective treatments at this time.
- With recent and future technological advances, newborn screening can also be used for more than testing for hematologic, endocrine, metabolic, and other genetic conditions. For example, newborn hearing screening is a widespread newborn screening procedure in the United States that currently does not use a blood sample or DNA-based testing technology (although hearing loss may be genetic in origin and blood samples may be used for DNA confirmation in the future). The future will bring more opportunities for early screening and systems integration.
- States will continue to be the policy innovators and primary regulators for health care, including insurance, public health, patient rights, and professional and facility licensure.

- Partnerships and collaborations between medicine and public health will be expanded and better developed. For newborn screening, immunization, and other services that operate at the intersection of clinical medicine and public health, effective collaboration is essential to achieving positive outcomes.
- Newborn screening will operate in a health care marketplace that depends on public-private ventures. State agencies will further expand private sector purchases and contracts for health-related services.
- The demand for consumer protections in health care will continue to be high; including demands for privacy and confidentiality protections of medical records and health information. These demands, along with parental opinions, will influence the future of newborn screening.
- Public perception of genetics in medicine and technology will lag behind scientific advances. Even among the better-educated general public, the perception of risks and benefits may differ from the views of health care professionals.
- Policymakers will continue to respond to concerns about the health of children and show some willingness to make investments in child health protections and prevention tools such as screening.
- Broader child health issues will continue to influence newborn screening systems; as newborn screening is only one part of child health surveillance, and infants with identified conditions are only one set of CSHCN.
- Health care cost containment pressures will continue to have substantial influence in health policy. If premiums for health coverage continue to rise, purchasers (eg, employers and government) and policymakers will take action. The response may lead to reduced coverage for new tests and treatments, greater inequities based on income level, and/or greater numbers of uninsured individuals and families. The result will be continued reduction in the quality of care.
- Health professionals will require ongoing training and education in newborn screening and new technologies. Additionally, pediatricians and other primary care health professionals who care for children should receive training on their role as the source of a child's medical home.

Advancing a National Agenda for Newborn Screening

The CORN guidelines^{7,9} and recommendations from previous expert panels and task forces form a foundation for advancing newborn screening. Despite some areas of disagreement (particularly on the topic of informed consent and parental permission), these documents together outline similar principles for conducting newborn screening (eg, the condition is serious, early screening would benefit infants, a reliable test is available, treatment is available, and early diagnosis and treatment are important to the infant). However, even when there is consensus, some state newborn screening systems have not applied these recommended standards and guidelines when setting policy and program structures.

In recommending model regulations and national standards, the Task Force recognizes that the translation of any models would have to conform to a state's particular infrastructure and infrastructure needs. The Task Force believes that public health agencies (federal and state), in partnership with health professionals and consumers, should continue a process that will:

- Better define public health responsibilities for federal and state public health agencies;
- Develop and disseminate model state regulations to guide implementation of state newborn screening systems (including disease and test selection criteria);
- Develop and evaluate innovative testing technologies;
- Design and apply minimum standards for newborn screening activities (eg, sample collection, laboratory quality, sample storage, and information systems);
- Develop and disseminate model follow-up, diagnosis and treatment guidelines, and protocols for health professionals and other participants in the newborn screening system;
- Design and evaluate model systems of care with services and supports from infancy to adulthood that are consistent with national guidelines for CSHCN (ie, family-centered, community-based, and coordinated systems of care);
- Design and evaluate tools and strategies to inform families and the general public more effectively; and
- Fund demonstration projects to evaluate technology, quality assurance, and health outcomes.

The Task Force has made further recommendations to address specific concerns and has identified needs for program and policy development in 4 key areas: Public Health Infrastructure; Professional and Consumer Involvement; Surveillance and Research; and The Economics of Screening. (Each topic is discussed extensively in later sections of this report.)

By outlining these recommendations, the Task Force seeks to further advance consensus. The Task Force recommendations call for change in many facets of state-based newborn screening systems. This work is intended to inform policy decision-makers about the possible strategies for enhancing newborn screening systems. The Secretary's Advisory Committee on Genetic Testing (SACGT) is expected to develop recommendations for the US Secretary of HHS regarding the oversight of genetic tests with respect to the accuracy, meaningfulness, and appropriate use. Newborn screening is among the issues the SACGT is addressing. Infant hearing screening, and other types of newborn screening, deserve similar attention from the federal and state policy communities. State legislators and executives face the challenge of deciding what tests, what testing technology, and what resources to use in protecting their pediatric populations.

Parents have served as advocates to advance newborn screening policy since the 1960s, and this con-

tinues to be an important role for them. Also, pediatricians and other primary care health professionals who care for children must participate in the development of guidelines for practice and policy. Joint leadership from government, health professionals, and parents will be essential if a nationwide approach to newborn screening is to be designed for the future, and if changes are to be implemented in each state.

Success of Newborn Screening

Newborn screening has been one of the nation's most impressive recent public health achievements and one of the most reliable components of child health services. The Task Force reaffirms that our nation's programs for newborn screening have improved the health and well-being of our children. The Task Force recommendations for newborn screening call for changes in many facets of these state-based systems, because the achievements of the past are not sufficient to carry newborn screening systems into the 21st century. Much has changed since most newborn screening systems were de-

signed 30 to 40 years ago. Success in the future will depend on the adequacy of our response to new genetic science, advances in knowledge about infant development, evolving biomedical technology, and changes in health care delivery and financing. Strengthening the newborn screening systems, as laid out in this blueprint, will require attention to the need for an improved public health infrastructure, the gaps in public and professional involvement, the challenging research agenda, and adequate financing. The intellectual and fiscal resources needed to achieve continued success are within our means and can be dedicated to the tasks ahead if there is political will to do so. Leadership from government, health professionals, and parents will be equally important to craft a national agenda for newborn screening and to implement changes in each state. Newborn screening can lead to early identification and treatment of about a dozen conditions today and perhaps scores of conditions by the year 2010. Well-functioning newborn screening systems are important to the 4 million US children born each year, and deserve the nation's attention.

II. PUBLIC HEALTH INFRASTRUCTURE

Newborn screening systems must be placed within an adequate public health infrastructure, since newborn screening involves more than testing. A screening test will be effective only if it is placed within an appropriate infrastructure that includes: education for the consumer and public, sample collection, laboratory tests, follow-up, diagnosis, appropriate treatment, information management, and system evaluation. The primary objective of each state's newborn screening system is to ensure that every newborn receives appropriate services. Public health agencies, at both the state and federal level, have a responsibility to ensure the quality of the newborn screening system. This section explores the history of newborn screening in public health agencies, the impact of new technologies in the evolution of screening programs, and the roles that can best be played by public health agencies in newborn screening systems.

The History of Newborn Screening as a Public Health Agency Role

Public Health Mission and Core Functions

To define the role of public health in newborn screening, one must understand how the level of scientific and technical knowledge, as well as public values, has changed over the past 37 years.

No single definition of the general role or mission of public health exists. Some describe public health as "population-based" activities that benefit everyone, as with prevention, or others see it as the health care of last resort. Although private organizations and individuals play important roles, governmental public health agencies have a unique function and responsibility to address this mission.

The IOM defined 3 core functions for public health agencies:

- Policy development—the responsibility to serve the public interest by promoting use of scientific knowledge in decision-making and policy development.
- Assurance—the responsibility to ensure that services are provided, either by encouraging action by other entities, requiring action through regulation, subsidizing services, or providing services directly.
- Assessment—the regular and systematic collection and analysis of information on the health of the community.⁶⁵

Public health programs and operations have conducted these roles since the 1890s. The first state and local health department laboratories concentrated on improving sanitation. Registries were established to track the spread of infectious diseases. Since that time, the role of detecting disease has continued to be an important one. Public health agencies were able to carry out activities that affected individual rights, such as these, because they operated under the authority of the state to protect the public's health.

Public health agencies have also been used throughout the 20th century as a base for diverse

activities including: home visits by public health nurses, health education, treatment of tuberculosis, childhood immunizations, as well as to directly furnish a broad package of clinical services. Between 1970 and 1990, many agencies used available resources to subsidize or provide services directly to medically indigent individuals, while maintaining the other core functions and responsibilities. During the 1990s, Medicaid was expanded to provide health coverage for low-income individuals, and was "privatized" through contracts with managed care plans.

Newborn Screening Becomes a Public Health Agency Role

With the advent of tests for PKU and other metabolic conditions in the 1960s, the responsibility to implement newborn screening systems was assumed by state public health agencies.^{12,17,18} Only public health agencies—using their authority to protect the public's health—could implement systems that would assess the prevalence of conditions, mandate newborn screening for all infants, ensure the quality and availability of testing, and provide follow-up on a population basis. Today, with new genetic technology and changing public opinions about the role of the government, the public health agencies' role in newborn screening systems is evolving.⁶⁶⁻⁶⁹

Challenges Facing Today's Public Health Agencies

State health agencies of the 1990s are different from those of the 1970s.^{65,70} They face the challenges of keeping up with new testing technology, responding to emerging infections and a resurgence of old diseases (ie, tuberculosis), coping with budget cutbacks or windfalls (eg, tobacco legislation funds), and operating in a new health care delivery system (eg, managed care arrangements, integrated health systems).⁷¹⁻⁷³ At the same time, state public health agencies remain charged with assessment, policy development, and assurance functions.

Challenges Related to Newborn Screening

Some challenges most directly related to newborn screening include:

- Laboratory capacity is sometimes inadequate. The methods used by some health department laboratories are in need of enhancement. In addition, public health laboratories are often under competitive pressure from commercial laboratories.⁷⁴
- Budget constraints make it more difficult for health departments to cope with the current workload, let alone with new tests that require additional equipment and personnel.
- Benefits of some screening tests have not been appropriately validated.
- State public health agencies screen for different conditions. These differences are not always based on the prevalence of the disorders in the respective states, or proof of the tests' utility and validity.
- Funding is insufficient for newborn screening quality assurance and evaluation, particularly for laboratory and database information systems.
- State policymakers possess an incomplete understanding of the conditions for which newborn

screening can be conducted, and/or of testing technology.

- Informing and educating consumers is often challenging, and meaningful public and consumer involvement is not always considered.
- Adequate funding is needed for comprehensive care by multidisciplinary teams in medical homes, including resources that ensure the availability of special formula, special foods, and other treatments for all affected children and adults.

Lack of Uniform Public Health Policy on Newborn Screening

Since newborn screening began, all states and territories of the United States have included newborn screening as part of their preventive public health system.^{75,76} Considerable variability exists in: the systems available for follow-up, the genetic conditions included as part of the screening system, the laboratory capability within the state, the treatment protocols, and the scope of follow-up services mandated as part of the newborn screening system.^{6,7,18,27,38,77} This situation highlights the need for uniform national policy on the selection of newborn screening tests, as well as common guidelines for newborn screening systems. Without nationally observed standards, infants across the country do not have equitable access to newborn screening, and its potential benefits. State legislators, health commissioners, and newborn screening system managers benefit from nationally recognized standards and guidelines by having recognized and well-considered benchmarks for the development of their programs.

The Task Force's Response to These Challenges

A continued role for state health departments in management, coordination, and evaluation of newborn screening programs is vital to sustaining and improving newborn screening systems. The Task Force concludes that a public health role is essential to continue newborn screening programs at their current levels. In facing current and future challenges, states and their public health agencies need to address the following questions:

- What steps are necessary to assist state policymakers in making decisions about tests and testing technology?
- How could a national, minimum set of newborn screening tests and standards be developed for use by states and their public health agencies?
- How can quality assurance and evaluation be better financed and utilized by public health agencies?
- How can public health agencies best carry out their quality assurance responsibilities in conjunction with private sector health care professionals, laboratories, and other entities?
- How could data and information efforts be improved to ensure the follow-up, tracking, and evaluation needs of newborn screening systems?
- What is the role of public health agencies in coordinating these efforts to ensure that they serve

families in the most efficient and effective manner?

- How can public health agencies ensure that the pediatrician or primary care health professional who is the source of the child's medical home receives newborn screening results in a timely and efficient fashion, even when the results are negative?
- How can public health agencies play a more active role in long-term management and follow-up from infancy to adulthood?

Designing and Developing Newborn Screening Systems

Decisions Regarding Tests and Testing Technology

In all states today, every infant is screened for 2 disorders: PKU and congenital hypothyroidism.^{6,7,9,18,30,48} Beyond these 2 tests, there is inconsistency between states in the panel of conditions screened. In addition, new advances in science and technology are continually making it possible to screen for additional conditions. The decision about which tests to include in a newborn screening panel is becoming increasingly complex. As a result, one role of the public health agency is to ensure that adequate data are available to decide whether a screening test should be included in the repertoire of routine tests.

If tests are outdated and need modification, or if the state public health agency feels that tests should be added or removed, challenges may exist in implementing these changes.^{78,79} A number of state programs offer tests prescribed by law, and must seek legislative change before making program change. In this case, it is preferable to seek legislative authority to allow program change through the rule-making (ie, regulatory) process. Many programs already have laws allowing program changes by rule (regulation).^{6,18,23} To add structure to such program change, it is preferable to adopt guidance for such considerations and debates. In accordance with the CORN guidelines for newborn screening systems,⁷ newborn screening program guidance in each state should include defined parameters such as:

- Demonstrated value to the affected patient and to the public through screening, detection, diagnosis, and treatment in a pilot program;
- A publicly accepted mechanism for funding the change which ensures that screening, follow-up, diagnosis, and treatment services will be available even if the family is unable to pay;
- Demonstrated cost utility, showing benefit in quality-adjusted years of life and reduced public health impact (prevalence × severity × effectiveness of intervention = public health impact);
- A mechanism for evaluating and ensuring quality throughout all elements of the screening system^{80,81}; and
- A system for educating all stakeholders as to the benefits of the program and its changes.

The Human Genetic Society of Australasia also defined parameters for inclusion or exclusion of con-

ditions screened for newborn screening programs.⁸² These categories include:

- Recommended for screening (a demonstrated benefit from early diagnosis exists that is balanced against financial and other costs, and for which suitable tests and follow-up services exist);
- Recommended if resources permit (a demonstrated benefit from early diagnosis exists that may not be balanced against financial and other costs depending on the available technology, the frequency of the disorder in the region, and other local circumstances);
- Pilot-screening recommended (benefit to the individual from early diagnosis appears likely, it is likely to be balanced against financial and other costs if suitable technology is available, there are tests available that are likely to be suitable, and there are follow-up services available);
- Screening tests are available but not currently recommended (proof of advantage from early diagnosis is absent or uncertain or the test is unsuitable or does not detect those cases in which there might be an advantage); and
- Conditions that may be detected incidental to screening for a recommended disorder (properly constituted research programs into the utility of screening for the disorder is encouraged).

Developing Adequate Follow-up Systems

Deciding which screening tests to include is just one aspect of the newborn screening system. To attain the greatest possible benefits of newborn screening, careful follow-up and continuity of care must also be ensured.^{7,9}

The role of state and local public health agencies in the initial follow-up of newborn screening varies widely.^{6,19,77,83-89} Some states assign the laboratory (public or private) the responsibility to communicate results to the health professional or facility that will follow-up with families. Other states provide active support by using local health department staff (usually from Title V MCH programs) to identify the medical home, locate the family, or communicate test results. When a child's family cannot be readily located, follow-up through mail, telephone, or direct contact through home visits may be necessary to ensure that a diagnostic test is done and treatment is initiated if warranted. Other state-financed follow-up activities may include public health nurses to collect blood specimens, nutritionists to help families establish and maintain dietary control for their children, and social workers to give support to families of affected children.

If an infant is identified and confirmed as having a specific disorder, follow-up with pediatric subspecialists and pediatric subspecialty clinics is often needed. In some cases, networking relationships between pediatric subspecialists and the infant's pediatrician/primary care health professional already exist. For example, some states simultaneously share sickle cell disease, congenital hypothyroidism, and PKU test results with the infant's primary care health professional and a pediatric subspecialist (eg, hema-

tologist, endocrinologist, or geneticist).⁴⁷ Health care professionals report that such links, through the newborn screening system, can simplify the follow-up process.⁴⁷

Follow-up of newborn screening tests is an activity that is performed by many health departments today.^{11,25,65,88,90,91} Most consider one of their roles to be providing or "enabling" support services (eg, care coordination, transportation, and information). This enabling role, that assists families seeking services and other public health agencies, is a base for home visiting programs. Evidence indicates that families and health professionals welcome this type of support. Generally commercial laboratories have not provided the same type of support services and assurance function essential to the newborn screening system.

Developing Newborn Screening Systems Through Education and Collaboration

Another public health agency role is to increase awareness of newborn screening among health professionals, parents, and the public. The success of newborn screening systems depends on the knowledge and behaviors of these individuals. An improved understanding of newborn screening and genetic medicine, and the benefits of the newborn screening public health program are essential.

In addition to providing education to health professionals, parents, and the public, collaboration among these groups, facilitated by public health agencies, is crucial. Multidisciplinary participation in newborn screening program advisory boards is one way that this collaboration can take place. The seamless integration and thoughtful collaboration among these participants is of vital importance to the smooth functioning of a universal newborn screening program. Partnerships must be maintained, so that the system's effectiveness can be sustained. (For further discussion, see Section III: Professional and Public Involvement.)

Quality Assurance and Evaluation

Ensuring the Quality of Newborn Screening Laboratories

Laboratories performing testing, in the public interest, are generally driven by 2 principal factors: cost-efficiency and quality. Ideally, newborn screening testing is inexpensive, produces high-quality results, and is technically advanced. In reality, it is often difficult to balance all of these factors within the political and economic environment of a state and a public health program.^{7,14,29} Therefore, it is incumbent on all programs to monitor laboratory performance and technological progress. It is thought that to maintain optimal quality, sufficient positive testing results should be encountered so that a positive test is easily recognized. There is no universally accepted standard in this regard, and high-quality laboratories exist with both low and high volumes of testing. In newborn screening, it has been recommended that the threshold number of samples should be 30 000 annually.⁷

In almost all state and territorial newborn screen-

ing systems, a public health laboratory provides testing.^{6,14} One potential problem is a low volume of cases and related cost and quality issues.⁹² In these cases, solutions can be sought jointly between the program and the laboratory. Some programs have found that laboratory regionalization and laboratory contracting offer possible solutions to this dilemma. Regional laboratories exist where states have agreed to pool their testing volume into a single laboratory, to maximize economies of scale.^{26,93} Other states use contractual arrangements with private or public laboratories. This approach may reduce costs or provide additional capacity not otherwise available. In either case, it is the responsibility of the state health agency and its newborn screening system to ensure the highest quality laboratory services for its constituents through laboratory monitoring and quality assurance procedures.

Today, all newborn screening testing must be performed by laboratories that meet the requirements of the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88), which include criteria for quality control and proficiency testing programs.⁹⁴ Proficiency testing is a tool used to evaluate the quality of a laboratory's testing process. This involves a monitoring organization sending proficiency testing specimens to laboratories on a periodic basis, usually quarterly. Proficiency testing specimens are then handled and analyzed in the same manner as patient specimens; with results sent back to the monitoring organization for evaluation. This testing helps to ensure the quality of each laboratory's measurement process. Laboratories must satisfactorily participate in a Health Care Financing Administration (HCFA)-approved proficiency testing program, if available, for each laboratory method they use to analyze human specimens.

Special expertise in dried blood spot technology is required in both newborn screening testing and quality assurance. Further, because quality assurance services would be provided to a small number of public health laboratories, it was thought that it would be burdensome for participating state laboratories to provide sufficient fees to support a national quality assurance effort. Therefore, more than 20 years ago, the NAS recommended that a single laboratory within the CDC be responsible for maintaining the proficiency of the regional laboratories conducting newborn screening for metabolic disease.²⁰ The CDC pursued this recommendation when the Genetic Services Branch, MCHB, HRSA offered to help support the development of a national quality assurance program at the CDC, which has come to be known as the Newborn Screening Quality Assurance Program (NSQAP). The NSQAP has enabled laboratories to meet the CLIA quality-assurance requirement for verifying test accuracy. This was particularly important in the absence of an HCFA-approved proficiency training program for newborn screening. This collaborative effort between the HRSA and the CDC (with the cooperation of the APHL) was based on recognition that newborn screening is a major public health effort mandated by laws in most states.

The HRSA's 20-year funding for the CDC's oper-

ation of the NSQAP ended in 1999, based on a recognition that emerging newborn screening technologies, such as DNA-based testing, required the involvement of the SACGT and other HHS agencies—the Food and Drug Administration, the HCFA, the National Institutes of Health, and the CDC—to address the regulatory and research needs related to quality assurance.

In the absence of HRSA funding for the NSQAP, a new mechanism for providing oversight and assuring quality in laboratories nationwide must be developed and funded. Moreover, as new screening technologies and modalities are put into practice, ensuring quality for all children in newborn screening systems depend on such a nationwide effort.

Evaluation of the Newborn Screening System

States play an active role in developing the structuring and financing mechanisms for quality assurance, accountability, and oversight of newborn screening systems. Although many state MCH programs, using their federal Title V Block Grant and state matching funds, play a key role in quality assurance for each of the first 4 components of the newborn screening system (screening, short-term follow-up, diagnosis, and treatment/management), the fifth component, evaluation will need to be addressed.

Public health agencies have a responsibility to evaluate the performance of the newborn screening system. This responsibility was broadly outlined by the IOM in 1987, and legislatively by the Title V Social Security Act for MCH programs.⁹⁵ For example, the new guidelines for state MCH programs (developed in response to Government in Performance and Results Act requirements) set out national performance measures for states. In addition, states have an opportunity to set additional performance objectives based on their needs and priorities, and some states use additional performance measures related to genetic conditions, birth defects, and/or newborn screening.

The CORN guidelines specifically emphasize the importance of evaluation in achieving the goals of newborn screening systems and ensuring that they operate in the most effective, efficient, and cost-effective manner.^{7,9} This component includes process evaluation of the state public health activities, as well as outcomes evaluation of the newborn screening system overall. At a minimum, state health agencies must complete a review and evaluation of their newborn screening activities (internally or externally). This includes quality assurance elements such as review of laboratory quality, appropriateness of specimen storage methods, rates for completion of repeat testing, and rates for completion of follow-up. Furthermore, current HRSA consultative program reviews, through its cooperative agreement to the National Newborn Screening and Genetic Resource Center, should be continued.

Program evaluation and quality assurance mechanisms in newborn screening systems need to be strengthened. On a population level, it is clear that mental retardation attributable to PKU and congen-

ital hypothyroidism, and mortality and morbidity from sickle cell disease in early childhood have been reduced.^{40,96-98} Evidence indicates that neonatal morbidity and mortality from maple syrup urine disease and galactosemia also have decreased.⁹⁶ At the same time, accurate and timely data are not available to measure the proportion of infants screened, proportion of infants with positive tests promptly and adequately followed-up, or success in terms of prevention of disability or other morbidity and mortality. On an individual level, data are not available to determine the range of functioning of affected children at various ages, the relation of function to care received, and the other benefits and risks (eg, parental anxiety, effect on unaffected siblings).

States should maintain ongoing outcome evaluations. State public health agencies play a role in defining performance and outcome measures. For example, under the HRSA Title V MCH Block Grant Program, state health agencies are accountable for reporting on 18 performance measures, including 4 that are directly related to newborn screening (see Section IV: Surveillance and Research). Additional state and local measures for newborn screening systems might focus on outcomes such as survival, and health and functional status; process factors such as time from test to diagnosis, and percent of repeat screens completed; and quality-related factors such as parental involvement and satisfaction, and number lost to follow-up in the course of specialty care.

Economic measures for cost-effectiveness or cost-benefit studies have been used in the past to assess the appropriateness and social utility of newborn screening. Screening for certain disorders, such as PKU and congenital hypothyroidism, have been shown to be cost-effective. However, economic analyses and evaluations must take into account that, while screening may save the lives of some infants, the long-term care costs will sometimes be higher than not screening. Thus, the use of cost-savings as the justification hinges on having a treatment that reduces long-term costs. Caution is warranted in only using economic measures as evaluation tools or outcome indicators (see Section V: The Economics of Screening).^{5,9,99-103}

Federal grants could be used to stimulate newborn screening information systems with an emphasis on outcome measurement and evaluation of effectiveness and cost-effectiveness. Such grants might provide incentives and start-up funding for outcome data collection systems, development of uniform data sets, and similar activities. As the health care system evolves—with the application of genetic medicine, new testing modalities, new delivery systems, and new technological tools to manage data and information—states face substantial challenges and have major opportunities to carry out the role of quality assurance.

Ensuring the Quality of Private Sector Activities Related to Newborn Screening

Private professionals and facilities carry out a number of newborn screening activities. These include specimen collection in hospitals, specimen

transport by private courier, laboratory tests by private laboratories, follow-up by private contractors, diagnosis and treatment at private specialty centers, and research by private institutions.¹³ Where the state health agency has only indirect responsibility, it has legislative and regulatory powers to ensure newborn screening system quality.^{18,19,53,104} This may come in the form of licensure requirements, reporting requirements, public health guidelines, contract specifications, and so forth. State public health agencies must develop collaborative approaches and linkages to private physicians, hospitals, laboratories, and others to ensure optimal coordination.

Integrating and Coordinating Related Programs

A Review of Related Programs

Public health agencies and other government programs have multiple programs designed to serve infants in the first month (neonatal period) or first year of life.^{105,106} The following programs are among those that logically could be connected to newborn heelstick screening programs. Each provides screening for other conditions, includes follow-up and tracking components, or is aimed at serving CSHCN.

Programs screening infants for other health and developmental risks

Prenatal screening and follow-up. Screening tests done prenatally may require follow-up treatment of the newborn infant.^{102,103,107-109}

Newborn hearing screening. An increasing number of states are implementing universal newborn hearing screening, shifting from policies that had previously emphasized hearing screening only for those infants with recognized risk factors for hearing deficits.^{31-33,84,110-114}

Supplemental Nutrition Program for Women, Infants, and Children (WIC). Substantial proportions of pregnant women and newborn infants receive nutrition support through the WIC. (In some states and cities, from 50% to 75% of infants meet income eligibility guidelines for the WIC.) Screening for nutritional risk is a core function of the WIC programs, and some also screen for immunization status and/or development risk.¹¹⁵ Historically, WIC programs have supported formula for management of PKU (ie, Colorado).

Outreach, case management, and home visiting programs. Child health programs that seek to identify children with varying levels of social or medical risk may involve outreach, case management services, or home visiting. In some areas, public health nurses may seek to provide a home visit for a large proportion, or all, infants and families shortly after birth. Such services may be a continuation of support initiated for mothers in the prenatal period.¹¹⁶⁻¹²¹

Programs for infants with or at risk for special health care needs

High-risk infant follow-up programs. Many states provide programs through which children discharged from newborn intensive care units receive

follow-up services and may be enrolled in special developmental follow-up clinics.¹²²⁻¹²⁴

Early intervention programs. PL 99-457 and subsequent amendment in the Individuals With Disabilities Education Act led to creation of programs designed to identify and provide services for children birth to age 3 with, or at risk for, potentially disabling conditions. While states may choose among the categories of children to be served, screening for eligible children and development of an "Individualized Family Service Plan" for follow-up and treatment is required in every state. These very young CSHCN may be linked to both health care and related developmental and educational services.¹²⁵⁻¹²⁷

State genetics services programs. Genetics programs may provide evaluation, diagnosis, long-term treatment, and case management for children with genetic disorders, including those identified by population-based heelstick newborn screening and birth defects registries.¹²⁸

Registry and data programs that include infants

Vital registration. Birth certificates are increasingly filed electronically. These electronically filed certificates may serve as the foundation for an electronic health record, including newborn screening status, and might be populated from newborn screening contacts.

Immunization registries. Infant immunization services may begin in the newborn nursery and continue throughout life. With substantial federal support and the involvement of private foundation and corporate resources, states are developing computerized immunization registries, using electronically filed birth certificates as the basis for initiating entry into the registry.¹²⁹

Birth defects registries. Increasingly states use birth defects registries to identify children with congenital abnormalities that require treatment and follow-up, to study the causes of these conditions, and to plan for services.¹³⁰

Challenges Involved in Coordinating Programs and Information Systems

Publicly funded infant and child health programs often operate independently of one another. The resulting duplication of effort can increase costs, burden families and health professionals, and create redundancy in data management systems. Improved coordination and integration of information systems is needed.^{131,132}

State agencies attempting to coordinate infant or other public health programs face a variety of challenges. These programs serving infants each operate with potentially varying time frames (ie, filing electronic birth certificates may take 2 to 3 weeks, but data for newborn heelstick screening needs to be entered within days of birth), definitions of eligibility (ie, universal heelstick screening versus means-defined WIC eligibility), demands and constraints imposed by categorical funding agencies, and priorities. In addition, they may be administered by different agencies within state governments.

As a result, services may not be well-integrated or coordinated. This can lead to the inefficient use of resources and frustration among families who are frequently asked to provide the same information on multiple forms of varying formats or categories. Information systems that support these programs may be insufficient, redundant, or independent of one another. Program integration and coordination cannot be achieved without a substantial new investment in infrastructure, and without addressing complex policy issues such as the confidentiality of health information.⁹⁰

Ironically, one of the unintended effects of this lack of coordination and/or communication among programs and data systems may be a form of greater confidentiality protection; the current system does not allow easy aggregation of personal information. This scenario leads to the following questions: 1) What is the optimal framework for integrating or coordinating public health systems for newborn assessment and follow-up? and 2) What is the role of information systems as part of efforts to improve program coordination? Technically, it is now feasible to link data systems; however, ensuring the proper use of data and adequate privacy protections may be difficult. Parents, health professionals, program managers, and public health officials may each have different goals and perspectives.^{132,133} Thus, in considering whether to integrate programs and their information systems, and how to go about this, it is essential to take into account the benefits, as well as the liabilities and costs to each group.

The value of efforts to link, coordinate, and integrate programs should be measured against the following criteria:

- Is duplication of effort reduced?
- Is the knowledge of resources and services improved?
- Is access to resources and services improved?
- Is the quality of services for children and families improved?
- Can appropriate privacy and confidentiality protections be ensured?
- Is the work of service and health care professionals facilitated?
- Is program management improved?
- Can improvements in public health be documented?
- Is there an improvement in child health?

Family perspective. Priorities from the perspective of families are likely to include:

Access to relevant information about the child. Parents and families are not apt to be concerned about the architecture of information systems. However, they are interested in having the information they need to make informed decisions in the interest of their child's health.^{134,135} They also desire timely access to various forms required for documentation of need or service, such as documentation of immunizations for school enrollment. In some instances, parents may have to balance their conflicting desires for easy access to services and protection of privacy (ie, a reg-

istry that gives ready access to immunization records requires that parents give permission to store the record).

Services ensured with continuity. A family's primary concern is that access to services is ensured, and that the array of services that children require be provided as seamlessly as possible, with minimal effort required in negotiating the system of care. A family also needs to know what services are available as they make choices for their child.

Privacy protection. The protection of privacy is often a paramount concern among families. Some may object entirely to their child being included in a government-sponsored registry.

Health care professional's perspective. As advocates for their patients, health care professionals will share many of the same interests as their patients and the patients' families. Health care professionals also are likely to have these additional interests^{136,137}:

Timely and ready access to accurate information about their patients. The health care professional wants the relevant screening information about that child readily available. For some professionals, or their staff, whether data are available through electronic systems may be less important than simply being ensured that the information can be obtained. For others, access to electronic child health records would facilitate their work. To the extent that computerized and other electronic systems are being developed as sources for program information, the health care professional (or staff) would prefer to tap into a single system to obtain data from different programs, rather than having to check multiple data systems to obtain information. For example, information from a single point of contact would ideally include: immunization status, and the results of hearing screening and heelstick screening. Easy access to equivocal, positive, or negative results of newborn screening is desirable, but is only one type of information a medical home may need.

Avoiding missed opportunities for follow-up at multiple points of contact with the child. Many children receive services at multiple locations or facilities. Ideally, information would be available to each health care professional, as necessary. Moreover, each professional should be aware of the need for follow-up on newborn screening and other conditions, regardless of the purpose of a particular visit. For example, if one of your colleague's patients is being seen in your office, you should have the ability to identify that the child needs a repeat PKU screening test, or that the child has failed their first hearing screen. This will allow the health care professional to take advantage of the opportunity for follow-up.

Minimizing duplication. Health care professionals and their staff, including hospital staff, are often frustrated by having to complete multiple forms requesting the same or similar information.

Minimizing liability. Health care professionals may be concerned about their liability if a registry exists. What is their responsibility and liability for checking a database to determine if a child needs a particular service? What is their responsibility and liability for

updating a registry after a patient encounter? How timely should those updates be?

Compatibility with existing systems. Many health care professionals have installed computerized office management software. Incompatibility between office and registry software could lead to extra time and costs.

System perspective. The "system" refers to the agencies or organizations that have the following responsibilities: the health of populations living within certain geographic boundaries, the health of those who receive care at a particular facility, and/or the health of those who are enrolled or covered by various insurance programs.¹³⁸ For agencies or organizations with these broad responsibilities, the ideal would include:

Capacity to monitor system performance. This includes the ability to monitor screening coverage, follow-up rates, and health outcomes affected by screening and care programs. It would also include the capacity to provide feedback to individuals or facilities responsible for managing or providing services at each stage in the screening and care cascade. This would enable identification of strengths and weaknesses in the programs to improve overall system performance.

Promotion of collaboration across agencies and organizations. Screening programs encompass a mix of public and private providers; from hospitals where screening tests are performed, to laboratories, to clinics that provide follow-up services. The information system that accompanies a screening program should foster communication and collaboration across the agencies and organizations from family to follow-up program.

Public health monitoring. Public health agencies have a responsibility to track trends in the occurrence and pattern of diseases in the populations they serve. The information system should allow monitoring of the prevalence of disease and the definition of the impact of the screening program on morbidity. It should also allow identification of disease in children not identified by screening (ie, "missed" cases), as well as trends in false-positive results.

Optimal use of resources. Multiple entry of the same or similar information into data systems for different programs represents a duplication of effort and thus extra cost.

Health services research. Monitoring the performance of the overall screening program may yield generalizable information that can be used not only locally but also by others to improve programs.

Data access and confidentiality. Public health agencies have a legal mandate to collect information about programs that they support and diseases that are under their jurisdiction. This requires appropriate access to health information. It may or may not require access to information with personal identifiers. When personal identifiers are stored with health information, it is essential that security measures and confidentiality policies, which protect against unauthorized access and violations of privacy, be in place.

Barriers to Program Integration

There are a variety of challenges to improve the integration of data systems that support different programs. These challenges include state variations, program-specific systems, costs, independence of heelstick screening programs, and public concerns about government data systems. A number of these issues are being addressed as states implement immunization registries. Topics being addressed in developing these registries include development of policies that define politically permissible levels of integration with other programs as well as responsibilities and liabilities for using and updating registries by health professionals and others.

The current system of categorical programs for newborn health, including independent information management systems, may serve the objectives of individual programs. However, on a broader level, it is inefficient, requires collection of duplicative information, and leads to fragmented services. As a result, there are increasing calls for integration of programs and information management systems. There is an opportunity to take advantage of new information management technologies to improve coordination among the various components of the newborn screening system, as well as improve integration between newborn screening and other related programs.^{11,129,139,140} Efforts to improve the internal or cross-system integration of newborn heelstick screening programs, should be done with careful consideration of program objectives and responsibilities at each level of the cascade of activities, from initial screening to long-term follow-up to system evaluation.^{7,9,18}

Response of the Task Force

The Task Force supports efforts to improve the integration and coordination of public programs that serve infants. The current approach to newborn programs has inherent costs arising from duplication of information collection and fragmentation of activities. Efforts to make programs more cohesive have associated costs as well. Given these costs, initial efforts toward improving integration and coordination should focus on a core group of activities and build, to the extent possible, on existing and successful state models. Although states may be the location for pilot efforts, national leadership and support can assist in development of new models for program integration. Two strategies are sound first steps toward improved coordination and integration:

Assess status of state newborn screening systems

Information is needed on the status of state newborn screening systems. Within heelstick screening programs, information is needed on the capacity to manage and integrate information at each stage of the system. More broadly, information is needed on the relationships among newborn programs, particularly the relationship between screening programs and immunization registries. Substantial effort toward development of information systems is being made in a number of states, including activities funded by the CDC through the development of

immunization registries. In October 1998, the directors of the CDC, HRSA, and HCFA sent a letter to state health and Medicaid directors in support of states' sharing of information across programs, and states' use of categorical funds to enable infrastructure development. To support the improvement of newborn screening systems, it would be useful to know how, whether, and to what extent these programs are involved in activities that are supporting infrastructure development and information-sharing.

Support program integration models

Grants from the HRSA could facilitate and foster the involvement of newborn screening systems in infrastructure development activities in states. Flexible grants would permit states to take advantage of individual strengths and assets. Such grants should encourage states to consider integration of heelstick screening programs with a core set of other newborn programs, including birth registration, immunization, newborn hearing screening, and possibly the WIC program. Because these various activities are supported by different federal agencies, it would be important for the HRSA to collaborate with these other federal agencies such as the CDC and HCFA in developing the grant program.

Task Force Recommendations for Public Health Infrastructure Development

National leadership and federal support are critical to strengthening the public health infrastructure. Flexible funding to support experimentation with activities such as program integration is needed. States with the best practices may lead the way, but a national process to share and promote such practices can facilitate these innovative efforts.

- Federal agencies must take action to strengthen the public health infrastructure for newborn screening.
 - The federal government—acting through the HRSA, CDC, HCFA, AHRQ, NIH, and other agencies—should collaborate to provide ongoing leadership and support for development of newborn screening standards, guidelines, and policies.
 - As the federal unit with most responsibility for newborn screening system development, the HRSA should engage in a national process involving government, professionals, and consumers to advance the recommendations of this Task Force and assist in the development and implementation of nationally-recognized newborn screening system standards and policies.
 - Federal resources should be identified to sustain a NSQAP to assist state public health laboratories. Such assistance must be both sustained and expanded as states adopt new screening technologies and modalities.
 - The HRSA's MCHB should strengthen current mechanisms to improve coordination of infant health programs and initiatives within the state and/or between states, including continuation of

funding in support of newborn screening program reviews.

- State public health agencies should direct their newborn screening program to be consistent with professional guidelines and recommendations. Each state public health agency should take responsibility for systems development. Specifically, states and their agencies have responsibility to:
 - Design and coordinate the newborn screening system;
 - Adhere to nationally recognized recommendations and standards for the validity and utility of tests. State newborn screening systems have a responsibility to review the appropriateness of existing tests, tests for additional conditions, and new screening technology and modalities; and
 - Adopt standards for laboratories, health professionals, and health care financing plans based on nationally recognized standards and guidelines for follow-up, diagnosis, and treatment.
- State public health agencies, working under legislative authority, have the ongoing responsibility to ensure quality and evaluate program effort. States and their state public health agencies should:
 - Maintain a newborn screening system that has appropriate evaluation, performance monitoring, and quality assurance activities from initial screening, through follow-up, diagnosis, treatment, and services through adolescence and adulthood;
 - Conduct oversight of program operations, including those outside the public health agency, such as test analysis and tracking, private sector

collection and transmission of screening data, laboratory quality, and the quality of the diagnostic procedures and treatment programs at pediatric subspecialty clinics; and

- Monitor and evaluate program performance through collection, assembly, analysis, and reporting of data, including outcome evaluations.
- States and state public health agencies should implement mechanisms to inform and involve health professionals and the public. Each state should:
 - Develop a program advisory board that is multidisciplinary, involves pediatricians and other primary care health professionals who provide medical homes for children, pediatric subspecialists, and has meaningful representation of families and the general public; and
 - Design and implement public, professional, and parent education efforts regarding newborn screening.
- States and state public health agencies should provide support for coordination and integration of program activities, including information and services. This will require public-private, federal-state, and intrastate partnerships. States should:
 - Use public and private resources to fund demonstration programs that can serve as a testing ground for linking information and services in ways that improve the newborn screening system; and
 - Structure interagency coordination to maximize resources and to improve the efficiency and effectiveness of newborn screening systems.

III. PROFESSIONAL AND PUBLIC INVOLVEMENT

The smooth functioning of a newborn screening system requires the concerted and dedicated effort of its multiple stakeholders. These key stakeholders include health professionals, parents, and the public.

The Role of Health Professionals in the Newborn Screening Process

Newborn screening is one among a group of public health activities conducted in close cooperation with health professionals. Although public health and private medicine have a long history of "unstable coexistence," stronger linkages have been proposed and are increasingly valuable in the current health care system.^{65,95} Moreover, newborn screening and other public health programs targeted toward the care of infants, face the challenge of assigning responsibilities to a pediatrician or other primary care health professional who may not be identified in hospital records, or may not have been selected by parents at the time of birth. Even if that individual can be identified, he/she may not be well-informed about newborn screening, genetic conditions, infant hearing screening, and so forth.

Those who provide medical homes for children must understand the newborn screening system, apply appropriate professional standards to their practice, and assume responsibility for their role in that newborn screening system.^{46,47,64,141-144} Ideally, the pediatrician or other primary care health professional who is the source of a child's medical home should take responsibility for the coordination of the newborn screening process, from initial screening through diagnosis and treatment. Thus, involving these health professionals in newborn screening, including test decisions, follow-up, diagnosis, treatment, and evaluation, is of vital importance to the success of the system.^{64,144}

Roles Related to the Testing Component

Ensuring that all newborns receive appropriate screening tests is central to the effectiveness of any newborn screening program. The awareness, knowledge, and practices of health care professionals who provide obstetric and pediatric care are critical to appropriate screening. For infants born in the hospital, a blood specimen or other test information should be obtained from every neonate before discharge or transfer from the newborn nursery, regardless of the nature or status of the infant's feeding or age, and transmitted to the state screening system. Moreover, for those discharged early (before 24 hours), a repeat blood specimen for some metabolic screening is recommended in professional and public health guidelines. Preterm infants, those being treated for illness, and those born outside a hospital should have newborn screening tests done before the seventh day of life, and before any blood transfusion.^{9,46,47,142}

Roles Related to Follow-up

The rapid follow-up of the infant with a positive initial screening test is the highest priority. The fol-

low-up process requires timely analysis of test results, rapid communication with the state public health agency's follow-up staff, and communication to the hospital of birth, the infant's pediatrician/primary care health professional, and/or the pediatric subspecialist responsible for subspecialty follow-up and management.^{6,7,9} State legislation and regulations vary, but most programs require that a health care professional be notified of the test result. This may include the infant's medical home, the submitter of the specimen, the birthing facility, the physician of record, and/or the subspecialist responsible for follow-up. Programs should require notification of the parent or guardian as well.

When they are notified, pediatricians, family physicians, nurse practitioners, or others play a critical role in this process. They have a responsibility to ensure that any infant with a positive or equivocal screen result is located, retested, and has a diagnosis confirmed or excluded. Unfortunately, because of the rarity of most conditions screened with heelstick blood samples, many health professionals may not be aware of all aspects of the newborn screening protocols in their states. Although virtually all pediatricians indicate they receive positive screening results in a timely fashion, most do not receive the newborn screening results for all infants in their care.⁴⁷ In addition, the majority do not follow up to secure missing results from newborn screening, assuming that the screening test is negative. In these cases, there is no documentation of newborn screening test results.

When a screening test is positive and a diagnosis is confirmed, the primary care health professional has the responsibility to connect the child to the treatment and care management components of the newborn screening system. This is crucial to ensure optimal outcomes and to avoid preventable consequences of the disorder. The most effective methods of locating and following infants with positive initial screening results will depend on local conditions and resources. Public health staff, including public health or community-based nurses, may play an active role in finding, informing, or linking families. Whatever the method, information that identifies a primary care health professional to a specimen can help avoid delays in the follow-up process. The time frame for following infants will also vary by the type of disorder, and by the magnitude and probable significance of the screening test abnormality. Timely follow-up is important for all disorders but is especially urgent for maple syrup urine disease, galactosemia, and congenital adrenal hyperplasia; these disorders can be fatal if not treated soon after birth. While all positive initial screening results must be followed to resolution, every attempt should be made to minimize the anxiety of the family and the emotional and fiscal costs of the inevitable false-positive tests. The primary care health professional can provide counseling and anticipatory guidance to families as they go through the newborn screening follow-up process.^{9,46,47,69,144,145}

Roles Related to Diagnosis Confirmation

Confirmation of presumptive positive newborn screening test results is always necessary. This requires qualified clinical and laboratory assessment of the infant by a pediatric subspecialist and laboratory in a time frame appropriate for the disorder. All diagnostic test results, normal and abnormal, must be reported to the follow-up and evaluation components of the newborn screening system including: the pediatrician or other primary care health professional, the parents, the state follow-up program, and the state laboratory. Many conditions identified by newborn screening programs are complicated by clinical heterogeneity, and thus, specialized diagnostic interpretation and individualized treatment are required. All inadequate or equivocal test results must be considered for follow-up, until determined to be negative by repeat testing or diagnostic evaluation.

Roles Related to Securing a Medical Home

Every child should have a medical home where care is accessible, family-centered, continuous, comprehensive, coordinated, compassionate, and culturally competent.^{64,144} Prospective parents can benefit by identifying a medical home for their child by the end of the sixth month of pregnancy, thus facilitating access to necessary care for the newborn. When the medical home is identified on birth records, follow-up for newborn screening tests is simplified. For most children, the ideal medical home is a pediatric health care professional working in partnership with the child's parents. For children with diagnosed genetic conditions, the source of the medical home should be the most medically appropriate pediatric specialist or multidisciplinary team, working in partnership with a primary care practice. Each patient and family is entitled to the medical home that best addresses his or her specific health care, as well as primary and preventive, needs.

Role of the Medical Home Health Care Professional

The primary care health professional should:

- Review and be aware of the policies and procedures of their hospital regarding all components of screening including the collection and handling of specimens, recording of identifying information, and timely transportation of specimens to the newborn screening program;
- Establish an office protocol to retrieve results of newborn screening for all newborns admitted to the practice when scheduling the first appointment. If screening cannot be documented, then these infants should be screened;
- Follow positive screening results to diagnosis (ie, confirmed or excluded) and report back to the newborn screening system, including repeated screening and diagnostic test results;
- Recommend and ensure access to subspecialty care and care for other illnesses, understanding that this may need to be provided by pediatric health care professionals and facilities with appro-

- appropriate expertise for the child's condition and special needs, and may require additional financing;
- Assist the family in understanding the diagnosis, symptoms, and potential implications of the condition, as well as the availability of genetic counseling, family testing, and other family support services. Reassurance should be given to families when an equivocal or positive result proves to be false. Culturally and linguistically appropriate educational materials should be used;
- Coordinate a seamless integration/communication/partnership with the pediatric center of expertise and community services;
- Understand their clear and defined role in providing the medical home;
- Provide health care supervision and preventive care including immunizations, growth and developmental assessments, and patient and parental counseling about health and psychosocial issues;
- Maintain a central record and database containing all pertinent medical information about the child. This record should be accessible to the family and those involved in the child's care, but confidentiality must be ensured; and
- Participate in training and continuing education offered by state programs, and report information such as health outcome data to state newborn screening programs.

Roles of the Subspecialist/Subspecialty Center

Subspecialty health care professionals should:

- Be experienced and knowledgeable about newborn screening and the diagnosis of the conditions targeted by the newborn screening program;
- Be experienced in the long-term management of infants affected by chronic conditions;
- Designate subspecialty care teams that offer appropriate personnel and services, depending on an infant's condition. Examples include: medical expertise; other health care professionals, such as advanced practice nurses, genetic counselors, social workers, metabolic nutritionists, etc; service coordination/case management; and family support services including peer support and other services such as financial assessment and counseling;
- Formulate short- and long-term therapeutic goals, systematic data collection, and outcome evaluation with linkages to the state newborn follow-up program;
- Provide appropriate follow-up information to pediatricians and other primary care health professionals, families, and the newborn screening system; and
- Assume the role of the medical home, with families and in partnership with the primary care health professional, if appropriate.

Roles of the Public in the Newborn Screening Process

State oversight of newborn screening and other public health programs may be structured in a variety of ways. Legislative oversight to monitor compliance with state law is one level.¹⁴⁶ In carrying out

their oversight responsibilities, state officials should use mechanisms to involve consumers. At the state level, a combination of approaches may provide the most effective participation. Mechanisms for addressing specific questions or decisions might include public meetings, workshops, or focus groups.¹⁴⁷ A state commission or similar entity is valuable to conduct ongoing oversight of the newborn screening system.

Public involvement in newborn screening systems has been widely recommended. *The Task Force on Genetic Testing* recommended that: "Consumers should be involved in policy (but not necessarily in technical) decisions regarding the adoption, introduction, and use of new, predictive genetic tests."²⁹ The CORN calls for at least one advisory committee that includes consumer representation in each state.^{7,9} A survey of state newborn screening systems, however, found that only 26 of the 51 jurisdictions reported having consumer representation on advisory committees.⁶ The roles and rights of parents in these public health agency programs varied markedly in terms of the type of information and the consent policies.

The NAS recommended in 1975 that public agencies use commissions to guide state decision-making.²⁰

The 1994 IOM report also recommended having a body independent of the state program or newborn screening laboratory. Such an advisory body would be involved in making decisions about new tests and testing technologies, program evaluation, quality control, and consumer protection activities. Membership of such an entity should include health professionals, experts, families affected by screening, and members of the broader public.²⁸

Roles of the Family

The Task Force recognized the importance of family involvement in newborn screening systems. Parents were involved in developing the recommendations of this report through membership on the Task Force, work groups, and by providing public comment. Based on the input received from parents and consumer advocates, the Task Force concluded that:

- Families should be educated about newborn screening. Information should be provided before birth or after birth. Information should be provided during the follow-up process, if the initial screening test is positive.^{23,148,149}
- Out of respect for the importance they play in the life of a child, the family should be recognized as an integral partner in the health care system. The family is responsible for adherence to recommended interventions and for maintaining contact with their primary care health professionals and pediatric subspecialists.
- The family should be involved in informed decision-making beginning with the initiation of newborn screening through the steps of the positive test result from the initial screening test, the confirmatory testing, and the enrollment in therapeutic interventions.

- Patient educational materials should be developed and reviewed in conjunction with families, be assessed for literacy levels, and reflect cultural competency.
- Families should receive information and counseling so that they are aware of the diagnosed condition, the potential associated co-morbidities, the short- and long-range treatment goals and interventions, and the availability of health care resources, including primary care health professionals, pediatric subspecialty consultants, genetic counselors, and state financial case management and assistance programs.
- Affected individuals and families should be involved in newborn screening program oversight (eg, advisory boards, review committees).

Professional and Public Involvement in Informed Consent

The Debate Over Informing and Consent

The issue of educating and informing parents about, and receiving permission for newborn screening is not simple. This issue has been debated since the first mandatory metabolic screening program for PKU began in 1963. In 1994, the IOM report raised concerns about the addition of unproven tests and made a recommendation for using informed consent when newborn screening tests or testing methods have not been studied carefully.²⁸

During the past 5 years, these recommendations have been discussed and debated by public health professionals, parent organizations, ethicists, and others. The IOM Committee's recommendations were introduced as "somewhat ideal scenarios" (preface) and it was recognized that such practices might not be realistic. Moreover, the Committee did not reject the idea of mandatory screening for conditions such as PKU or congenital hypothyroidism where tests and treatment have been proven safe and effective.

In response to the IOM recommendations, the Newborn Screening Committee of the CORN, the American Society of Human Genetics, and the Joint Committee on Professional Practices of the American College of Medical Genetics raised further questions about the practicality of implementing informed consent policies.¹⁵⁰⁻¹⁵³

Current State Practices

State policies regarding informing parents and parental refusal and consent vary widely. Forty-nine states have specific legislation that requires newborn screening; 3 states have provisions for informed decision-making.^{23,146,154} Currently, Maryland has a voluntary newborn screening program, Wyoming uses an informed consent model, and Massachusetts recently began using an informed consent process in a pilot newborn screening program. Most states permit parental refusal, but only under limited circumstances. Parents may not be told directly that they have the opportunity to refuse, and for some parents, mandatory offering may be confused with mandatory screening. In most states, it is routine practice to

accept parent refusals but not to ask for documentation (ie, with a form and parental signature).¹⁵⁵

There are several arguments in favor of not seeking parental permission for newborns screening.¹⁵⁶ First, and perhaps most important, is that screening and potential detection is in the interest of the child and the parents' objections should not hinder that screening process. This may be more compelling for PKU than for diseases where the benefits of screening would be less clear-cut, as with Fragile X syndrome.^{157,158} As most state newborn screening laws make accommodations for parents who refuse testing, this argument does not seem to be the basis of the current approach. A second argument is that it is not feasible or it is too costly to talk to parents and ask permission. In early studies of the Maryland newborn screening system, the cost and time involved in the Maryland program did not appear to be prohibitive. The current approach in Maryland is a simple "goodwill" informed consent for the total screening package and does not allow for separate consent or refusal for each disorder.¹⁵⁹

Shared Decision-Making as a Model for Informed Consent

An informed consent process for medical procedures and interventions is a basic expectation of the general public today. Although it is often equated with signing an "informed consent form," shared decision-making can occur without signing a form, and signing a form does not guarantee that shared decision-making or informed consent has occurred. Shared decision-making refers to a conversation, between the health professional and the patient/parent, where relevant information is disclosed. Most of the discussion between professionals and parents regarding the care of children is rather informal.^{107,155,156,160} Nonetheless, health professionals talk with parents not only because they have to, to treat the child, and not just because they may think that the parents will be more "compliant" if they buy into the plan; but more importantly because health professionals respect the independent and important role parents play. For this reason the Task Force emphasized the importance of the conversation, not the documentation to achieve shared decision-making.

The Task Force recommended that additional approaches to informing and educating parents be studied further. A greater emphasis on parental education may improve parent understanding and increase the number of parents who comply with recommendations for further testing and follow-up. Such education may also help parents deal with the anxiety associated with equivocal results, repeated tests, and false-positive results. Furthermore, informed decision-making is particularly important when the safety and effectiveness of some newborn screening tests and screening technology are still being evaluated. With the addition of new DNA-based tests, and the addition of screening tests for conditions for which the treatment intervention or the efficacy of the treatment intervention is unknown, the ethical, legal, and social demands to ob-

tain documentation of permission for newborn screening may increase.

The consensus of the Task Force is that the goals of newborn screening can be accomplished while acknowledging the role parents play in deciding what is going to be done to their children, and while also respecting the wishes of those few parents who object. The Task Force achieved a new level of consensus about consumer information, along with recommendations for future action. Parents need to be informed about the benefits and potential risks of the tests and treatments, the policy for storage and use of specimens, and the mechanism by which families will receive test results. Of particular importance in informing parents is their understanding of why they should respond to abnormal results, how to respond, and the possibility of false-positive results. Determining the best mechanisms to inform parents and promote screening then becomes the issue. All prospective parents should be made aware of the newborn screening process. One practical strategy for educating parents is for prenatal health care professionals to provide this information early on during the course of prenatal care. Ideally, this could be accompanied by educational material and/or videotapes provided during one of the third trimester prenatal visits, with a brief review by office or clinic staff.

Task Force Recommendations to Increase Professional and Public Involvement in Newborn Screening Systems

The *Task Force* recommends that:

- The pediatrician or other primary care health professional who, in partnership with parents, is the source of the child's medical home, should:
 - Ensure that all newborns admitted to their practice have received adequate newborn screening, and that appropriate documentation of this testing is present;
 - Follow positive screening results to diagnosis (ie, confirmed or excluded), including repeated screening and diagnostic testing;
 - Coordinate a seamless system of care with pediatric subspecialty clinics, tertiary care centers, and/or community-based providers, when a child is diagnosed with a disorder through newborn screening;
 - Maintain a central record and database containing all pertinent medical information about the child. This record should be accessible to the family and others involved in the child's care, but confidentiality must be assured; and
 - Assist the family in understanding the diagnosis, symptoms, and potential implications of a diagnosed genetic/metabolic condition, as well as the availability of genetic counseling, family testing, and other family support services.
- Parents should receive information (on behalf of their children) about newborn screening.
 - Prospective parents should receive information about newborn screening during the prenatal period. Pregnant women should be made aware of

the process and benefits of newborn screening and their right of refusal before testing, preferably during a routine third trimester prenatal care visit.

- Parent knowledge should be reinforced after delivery by educational materials and discussion as needed by the infant's primary care health professional and/or knowledgeable hospital staff.
- Prenatal health care professionals as well as the infant's primary care health professional should be knowledgeable about their state's newborn screening program through educational efforts coordinated by the state's newborn screening program in conjunction with a newborn screening advisory body.
- Written documentation of consent is not required for the majority of newborn screening tests, for example, those tests of proven validity and utility.
 - Parents should always be informed of testing and have the opportunity to refuse testing.
 - If after discussions about newborn screening with health professionals, parents refuse to have their newborn tested, this refusal should be documented in writing and honored.
 - If a newborn screening test is investigational or in the process of being developed, the benefits or potential risks have yet to be demonstrated, and identifiers are not removed from the specimen, informed consent should be obtained from parents and documented.
- Studies should be done to broaden understanding of the ways in which communication can be done more effectively for the benefit of consumers.
 - Pilot studies and evaluation research should be conducted to assess the potential impact of revised parental permission and informed decision-making policies.
 - Each state or region should, with input from families who have children with special needs and/or parent information centers, develop and provide family educational materials about newborn screening.
 - Evaluation of materials should be ongoing, par-

ticularly because of the changing demographics of childbearing, cultural changes, and rapid developments in genetic science.

- Parents have a right to confidentiality and privacy protections for the medical and genetic information in any type of newborn screening results. Based on nationally recognized standards and guidelines, each state should have appropriate policies and mechanisms in place to ensure families' privacy and confidentiality. Laws to guarantee genetic privacy and protect against genetic discrimination should benefit patients identified by newborn screening.
- States and the federal government should include public participation in medical policy-making. The SACGT provides a mechanism for public participation in genetic policy development at the federal level. Each state should establish and fund a newborn screening advisory body with public participation to advise on newborn screening policy developments.
 - Such an entity should include a broad range of public advisors representing parents, health professionals, third-party payers, appropriate government agencies, and other concerned citizens.
 - Such an entity should be empowered to advise state officials about screening for particular conditions based on accepted standards and be consulted about the development of related state regulations.
 - Such an entity should be involved in the review of new tests under consideration by the state and in the development of pilot programs for new tests.
 - Such an entity should be involved in the ongoing evaluation of all aspects of the state's process for newborn screening. Oversight activities should include a review of: testing, follow-up and treatment efforts; the impact on families of receiving a false-positive screening result; and the state's process for handling consumer input including grievances.

IV. SURVEILLANCE AND RESEARCH

Public health agencies must ensure adequate policies for surveillance and research related to newborn screening. Surveillance and research are important activities that impact the growth of the newborn screening system. Without surveillance activities, such as performance measurement or outcome evaluations, it is difficult to assess the degree to which a particular newborn screening program benefits infants. Without research to determine the effectiveness of new technology or to develop new screening tests, potential benefits to newborn screening systems may be lost.

Performance Measurement

State and federal public health agencies engage in both the collection and analysis of data in their assessment activities, and for a variety of reporting requirements. In particular, state MCH programs should be involved in the design, implementation, coordination, and evaluation of newborn screening systems, as they are the locus of responsibility for child health. Each state MCH program has a variety of care and services aimed at the population of CSHCN. Because children with conditions identified through newborn screening are a subset of CSHCN, achievement of the "National Agenda for Children With Special Health Care Needs" will improve newborn screening systems and services. The core objectives for outcomes of this National Agenda are:

- All CSHCN will receive regular ongoing comprehensive care within a medical home.
- All families of CSHCN will have adequate private and/or public insurance to pay for the services they need.
- All children will be screened early and continuously for special health care needs.
- Services for CSHCN and their families will be organized in ways that families can use them easily.
- Families of CSHCN will participate in decision-making at all levels and will be satisfied with the services they receive.
- All youth with special health care needs will receive the services necessary to make appropriate transitions to all aspects of adult life, including adult health care, work, and independence.¹⁶¹

The HRSA's MCHB has a key role to play in assisting states to work toward these objectives. The MCHB assists in measuring performance and stimulating the development of newborn screening systems and related information systems, with a focus on development of standardized data sets, outcome evaluation, and analyses of cost-efficiency and effectiveness. Federal guidance issued in 1998 established the HRSA's Title V Block Grant Measurement Performance System, and required that state MCH agencies report on a set of 18 national core performance measures. Among these core performance measures are measures directly related to newborn screening and the recommendations presented in this report.

These performance measures require each state to assess the extent to which they:

- Increase the percent of newborns in the state with at least 1 screening for each of PKU, hypothyroidism, galactosemia, hemoglobinopathies (eg, sickle cell disease) (combined).
- Increase the percent of newborns who have been screened for hearing impairment before hospital discharge.
- Increase the percent of CSHCN in the state who have a medical/health home.
- Increase the degree to which the state ensures family participation in program and policy activities in the state CSHCN program.¹⁶²

States also have defined additional performance measures that fit with their priorities, programs, and populations. State-defined indicators are selected to measure the percent of newborns who receive additional newborn screening tests, the rate of selected congenital conditions (for birth defects surveillance), and the percent of identified infants who have received follow-up care and treatment within the medical home.¹⁶³

The strategic goals and objectives of the MCHB are linked to these performance measures. In relation to newborn screening, the MCHB objectives aim to do the following by 2003: ensure that all newborns are screened, diagnosed, and provided treatment for disorders identified by state specific newborn screening programs; ensure that 50% of all children, including CSHCN, are enrolled in a medical home; and ensure that 100% of the major national managed care organizations have a mechanism to measure the quality of the components of a medical home for CSHCN. Other objectives aim to enhance research and surveillance capacity such as increased use of data and information, improved scientific knowledge base, and use of linked electronic databases.

Performance measures also have been developed for the private sector. For health plans, and the professionals and facilities that deliver care for their enrollees, the Health Plan Employer Data and Information Set (HEDIS) sets out performance measures.¹⁶⁴ The HEDIS is currently being used by a wide range of private and public (ie, Medicaid) purchasers who seek to measure the value and performance they receive for the dollars they spend on coverage. In terms of newborns, the HEDIS includes measures on immunization rates, low-birth weight rates, and length of newborn stay; however, it does not assess performance on newborn screening. Other measures are being developed in the private sector, including a set specifically for CSHCN.

In a health care system that demands increasing accountability from government, health plans, and health professionals, these goals, objectives, and performance measures help to define surveillance and research needs in newborn screening systems.

Program Evaluation

Setting Priorities for Data Collection

The integration of information systems would allow newborn screening program evaluation to take

place with more ease. Ideally, the information obtained by a newborn screening program would allow the description of:

- The number and percent of children
 - adequately screened,
 - with appropriate follow-up,
 - with false-positive and false-negative results,
 - with specific diagnoses, and
 - with appropriate care.
- The time between the newborn screen and the initiation of treatment.
- The long-term improvement in health status occurring as a result of screening, follow-up, diagnosis, and treatment.
- The number of children diagnosed with a condition missed by the screening programs and, where possible, an assessment of the reasons they were missed.
- The number and percentage of children lost to follow-up.

Improving Information Systems for the Purposes of Surveillance and Research

Data collection and analysis are necessary for surveillance activities, epidemiologic studies, program evaluation, and research. These activities require a strong commitment to developing and maintaining an adequate information infrastructure.

In considering the improvement of data systems for newborn screening programs and coordination with other programs, an initial state assessment, consisting of the following components, is necessary:

- The objectives of the program.
- The components of the system and responsibilities for managing each component.
- The collection and intended flow of information.
- The quality of communication among persons and facilities at different stages of the program.
- Procedures for follow-up (short- and long-term).
- Information required for evaluation of the program.

These components of newborn screening systems are outlined more fully in the CORN system guidelines.^{7,9} For other types of newborn screening, such as hearing screening, the strength and integration of information systems are equally important. Descriptions of these components in the context of an individual state program will enable a clearer articulation of the purposes of the information system needed to support these elements of the program.

Some broad concerns underlie the development of information systems, and these concerns assume greater importance as complex systems for record linkages and system integration are proposed. These include:

- Ensuring those information system procedures relate to program objectives.
- Defining time frames for data collection and feedback (eg, how quickly should data be accessible at each stage in the screening, follow-up, diagnosis, and treatment process).

- Defining reporting procedures (eg, what reports will be made, who will receive them).
- Ensuring commitment to maintaining systems.
- Ensuring that procedures for maintaining, transmitting, analyzing, and disseminating data conform to ethical guidelines and legal standards.

The Role of Record Linkages

Record linkages, or the process of relating information about individual newborns from different information systems, provides an approach to integrating information management within a program (eg, information from various stages in the service cascade) and integrating information across programs. In some instances, such linkages may not be required to meet specific objectives; instead, a capacity to synthesize information from multiple sources would be sufficient.

Issues to consider for record linkages or information synthesis include:

- **Short- and long-term information needs of the screening program (eg, screening and follow-up data).** This would include information needed to optimally serve families, to assess the newborn screening program, and to provide information that would improve the operation of screening and follow-up.
 - Definition of screening coverage requires a denominator, which is defined by the total number of live births. This would involve relating newborn screening data to the birth certificate file.
 - Assessment of health outcomes involves follow-up of infants with diagnosed disorders through use of medical records. This may require use of multiple data sources from health care professionals (eg, hospital discharge records, outpatient visits). Newborn screening systems alone often lack the authority and personnel to collect outcome data.
- **Integration with other data systems to minimize duplication and facilitate cross-program communication.** This would require definition of core data sets that could be better coordinated or integrated, (eg, electronic birth files and immunization registries). One example of a core data set is birth registration, newborn heelstick screening, newborn hearing screening, and immunization; these are activities that are initiated in the newborn hospital nursery and are universal (or likely to become universal). Information from the WIC program, which serves a large proportion of infants, and birth defect registries may be other data sources to consider as part of the core.
- **Definition of the purpose of record linkages and data synthesis.** The purpose and intended uses of a data system will have a profound impact on its level of technical complexity and cost, depending on whether the intent is to:
 - Allow retrospective program assessment using historical data, such as an annual assessment, or
 - Improve screening and care management through real-time data systems.

In proposing development of an integrated information system, there are multiple technical and logistic considerations that should be taken into account. These procedures for accessing and manipulating screening files include:

- **Distillation of records on samples to individual client-level data** (ie, ensuring that multiple screening or follow-up samples can be identified as belonging to an individual child).
- **Definition of variables and criteria that would be used to define linkages.** Criteria for associating records from heelstick screening to the birth file must be defined, including acceptable levels of unmatched (sensitivity) or mismatched (specificity) records. The role and definition of a universal health identification number is beyond the scope of this report but is critical to any discussion of the integration of health systems. Clearly, the use of a standard identification number would greatly facilitate the integration of data systems across newborn service programs. States have developed numbering systems that serve newborn screening programs and have piloted systems that would allow use of this number as a prototype for a broader, health identification number. In addition, substantial work is being done nationally in consideration of a standard health identification number. The implementation of such an identification number would not solve all problems in merging information across programs, because errors may be made in its entry into records or databases.
- **Consideration of the role of new technologies for identification and information storage.** In some hospitals "bar code" technology (eg, on wristbands and forms) is being used to facilitate and ensure identification of newborns. The use of scanning devices at the time that various procedures are performed to collect samples (heelstick), perform other tests (hearing screen), or provide service (immunization) offers one approach to integrating information management at the hospital level.

Another technology is the use of so-called "smart" cards, credit card-sized information storage devices that allow the creation of a highly portable record that would be carried by parents and updated or read by professionals at various points of service. This technology could support a highly decentralized information storage and retrieval system that, in itself, would support some of the above objectives (eg, improved health professional access to patient information) but not all (eg, public health monitoring) in the absence of linkage with more centralized systems.

Using an Evidence-Based Approach to Make Decisions About New Tests

Since the 1960s, decisions about which tests to use in newborn screening programs often have been made in an extemporaneous fashion, depending on recommendations from professional groups, patient advocates, state legislators, and newborn screening

programs.^{19,35,77,84,157,165-172} Only rarely, for example with screening for sickle cell disease, has the decision been based on empirical evidence of safety and efficacy from a clinical trial (and in that case, the clinical trial findings were related to the effectiveness of treatment).^{16,29,41} Surveillance and research are essential to provide the evidence needed for state-level decisions and nationally recognized standards.

The Task Force on Genetic Testing in their report, *Promoting Safe and Effective Genetic Testing in the United States*, gave particular attention to an evidence-based approach.²⁹ They recommended that a test must be determined to have analytical sensitivity and specificity before it is made available in practice. Clinical validation is the next step, with clinical sensitivity, specificity, and predictive value determined through study with a sample population that is representative of the test's target population. The test should also have clinical utility—that is, interventions to improve the outcome for the infant must be safe and effective.

In making decisions about which newborn screening tests to use and for whom, states need information. Pilot studies are an important tool in this process.^{59,173} Such studies might be undertaken by an individual state (eg, currently several pilot studies are underway in Massachusetts). For rare conditions, collaborative efforts between states will be needed to expedite data collection. Collaborative clinical trials (such as the prospective study of prophylactic penicillin with sickle cell anemia) may also be needed to evaluate the effectiveness of treatment and interventions. In all such studies, safeguards are needed to protect the confidentiality of the individual infants who are the source of the data.

The Task Force on Genetic Testing called for an active role by federal agencies, particularly the NIH and CDC, in supporting collaborative efforts to collect data on the safety and effectiveness of genetic tests.²⁹ Support might be in the form of funding, guidelines, and/or oversight.

Establishing Policies and Procedures for Use of Residual Blood Samples in Research

In the case of newborn heelstick testing, data collection and analysis activities also require that policies and procedures be in place to cover the use of residual blood samples for research. Such research might be related to new or existing newborn screening technologies, or to epidemiologic research relevant to clinical medicine and public health. In either case, state policies should determine storage conditions, uses, and consumer protections.

Almost all infants screened have residual blood samples retained by the state programs. Enough blood is obtained when performing heelstick newborn screening to permit programs to repeat tests when necessary. However, because repeat tests are not always necessary, and a repeat test may not use up the blood sample, the vast majority of infants screened (in excess of 95%) will have residual blood samples retained by the state programs. Currently, state programs hold these samples for variable lengths of time: 10 programs save samples for 21

years or more; 6 programs for 5 to 7 years; 2 programs for 1 to 3 years; 6 programs for 6 to 12 months; 21 programs for 1 to 6 months; and 5 programs for 1 to 4 weeks. Only 1 program is known to save the samples under optimal conditions for later use in biochemical analyses. Optimal storage conditions are much less critical for genetic analyses, and samples stored in many states are adequate for genetic analyses. The lack of uniformity between programs reflects uncertainty and debate over whether residual blood samples should be retained and, if so, for how long and under what conditions.^{6,174-177}

Potential Uses of Residual Blood Samples

The conclusions of the Task Force are predicated on 2 principles: 1) that residual blood samples are a valuable resource, and 2) that their use should be carefully managed to protect the interests of those from whom they are obtained. To achieve the maximum benefit from residual blood samples, and to ensure that samples are used to promote child, family, and public health, state programs (with input from the public) should thoroughly evaluate their policies and procedures. The retention of these samples should be guided by state policies that articulate the objectives of the storage and use of the samples, and include safeguards against inappropriate use. These policies should define the rationale for retaining and analyzing samples with or without identifying information. However, policies and protocols for the retention and use of residual blood samples should not hinder the primary function of newborn screening programs, which is the early detection and treatment of infants with conditions that the newborn screening program has targeted to screen.

Residual blood samples may be used for several purposes including:

- **Research related to new or existing newborn screening modalities.** As technology advances for newborn screening programs, new testing modalities will be developed for conditions included in current programs, and new tests will be added for other health conditions. Residual heelstick blood samples can be used to ascertain the validity of new testing modalities for existing conditions and of tests for new conditions. Identifiers are sometimes retained to enable follow-up contact with an infant's family if an effective intervention is available for children diagnosed with the condition.
- **Epidemiologic research relevant to clinical medicine and public health.** Public health officials need population-based data to determine the appropriate allocation of resources to care for children with specific conditions. A thorough understanding of many health conditions requires epidemiologic data on the prevalence of specific genetic or biochemical attributes in the general population. Residual newborn screening samples constitute a specimen bank of a large cohort of the population of states. As genetic technology advances, such a comprehensive bank, linked to basic demographic information, may be useful for certain types of research. The potential utility of

such a resource will need to be carefully evaluated because residual blood samples in this context will not be linked to clinical data on the children.¹⁷⁸⁻¹⁸⁶

- **Clinical or forensic testing.** For children who have moved and cannot be located, the heelstick blood sample may represent the only source of a biological specimen from a given child. The sample may be useful for forensic purposes. Testing of residual blood samples may be essential in the postmortem identification of a genetic condition that may have contributed to a child's death. At least 1 state has decided to store newborn blood spots indefinitely to permit identification of children who have been kidnapped.¹⁸⁷

Ethical Concerns Related to Use of Residual Blood Samples

Storage and use of residual newborn screening blood samples raise a number of practical and ethical challenges. Ethical challenges include the development of guidance regarding the use of residual blood spots for purposes other than those for which they were originally obtained. The protection of privacy and confidentiality among children and families is a serious concern. In the case of newborn screening, when blood samples are collected from infants as a matter of law, there is additional reason to ensure appropriate storage and use.^{175-177,188-191}

At the same time, residual newborn screening samples have been used to address important public health issues. The prevalence of in utero exposure to drugs and environmental agents; the allele frequency of genes associated with significant morbidity, mortality, or disability in infancy or childhood,^{66,157,192} and the prevalence of serious maternal or intrauterine infections have been determined in various populations by anonymous use of residual blood spots.^{178,179,183,184} Samples linked to outcome have been used to assess the feasibility of screening for various diseases of the newborn and infant, and to determine risk factors for birth defects and developmental disabilities.^{180,185,186,193} To date, there have been no published reports of misuse of residual newborn screening samples in research projects; however, the potential for use and misuse is expanding.

The Task Force recognized the ethical challenges in a new era of genetic science and the practical challenges related to cost, space, storage, and the development of databases to catalog large numbers of samples. The Task Force also discussed the potential value of these samples for research and also recognized that their use for research must include protections for the privacy and confidentiality of children and their families, as would be the case for any research with human biologic materials. There is active debate in the US health care community about the appropriate uses of residual human biologic materials. Policies and procedures for the use of residual newborn screening samples need to be developed in the context of this debate.

Defining Sample Categories

One factor affecting the level of risk associated with using human biological materials for research is whether a particular sample can be linked with an

individual. Commonly agreed on definitions that reflect the degree to which samples can identify an individual are important to building an understanding of how newborn screening blood samples are or are not protected. In its evaluation of residual blood samples, the Task Force defined 2 broad categories for use of residual newborn screening blood samples: *unlinked* and *identifiable* samples. Based on statements by the National Bioethics Advisory Commission (NBAC), the Task Force used the following definitions¹⁹⁴:

- Unlinked (sometimes called anonymous) samples lack identifiers or codes that can link a particular sample to an identified specimen or a particular human being. These samples may have originally been collected without identifiers, or the identifying information (eg, names, registration numbers) may have been removed; making it impossible to link the sample with the patient.
- Identifiable samples are either directly identifiable or coded with a link to identifying personal information.
 - Directly identified materials have identifying information (eg, name or patient number) attached and available to researchers.
 - Coded samples are numbered or labeled in a manner that does not allow a researcher using the specimen to identify the individual from whom the specimen was collected. However, a link between the code marker and personal identification information is retained, permitting patient identification for other reasons (such as family requests). In some circumstances, linkage information between samples and personal identifiers can be retained by a third party to strengthen safeguards for privacy and confidentiality.

An important topic of debate is whether consent for research is needed from the individual from whom biological materials are obtained. Although this question is not totally resolved, major efforts are underway across the country to develop mechanisms to inform patients and obtain their consent.

By contrast, 3 states currently require informed permission from parents for newborn screening itself. None of these states obtains specific permission for use of the samples for research purposes; however, the state of Maryland does inform parents in

an informational brochure that samples may be used for certain types of research and individual results will not be identifiable. The universal lack of permission for using bloodspots for research gives added weight to concerns about privacy, confidentiality, and discrimination.

The text and Table 2 below outline 2 broad categories for the use of residual newborn screening blood samples. Together, these reflect the conclusions of the Task Force about appropriate purposes, applications, and protections.

Use of unlinked samples. Unlinked samples may retain limited demographic information (eg, gender and ethnicity) to provide general descriptive categories in epidemiologic analyses. However, such information should not be sufficient to permit identification of an individual. Current national standards stipulate that epidemiologic research can be conducted without consent, as long as identifiers are removed. Parents should be informed that unlinked samples might be used for quality improvement purposes or for epidemiologic research consistent with the goals of newborn screening programs. Protocols for the use of unlinked samples in hospital and laboratory quality assurance activities need not be submitted for institutional review board (IRB) review. Legislative approval and regulatory guidance for research on unlinked samples should be consistent with the goals of newborn screening programs and public health efforts.

Use of identifiable samples. The Task Force concluded that parental permission should be sought for the use of identifiable samples in research to validate tests for additional diseases, or for epidemiologic research. Identifiable samples from newborns should be used for research only if: 1) IRB approval is obtained for the proposed research, 2) consent is obtained from the child's parent(s) or guardian for the proposed research, 3) newborn samples represent the optimal source of available tissue for the research, 4) unlinked samples will not suffice, and 5) acceptable samples from consenting adults are not available.

In accordance with current federal regulations regarding research involving children, use of such samples for research, that poses more than minimal risk, should be limited to activities that benefit the

TABLE 2. Classification of Biological Samples

Use	Unlinked	Identifiable
Focus	• Populations	• Populations to individual
Purpose	• Epidemiologic studies • Quality assurance • Test refinements	• Medical and clinical studies for individuals • Clinical validation of tests for additional disease • Legal and forensic work
Consent process	• "Right of refusal" permission routinely used in newborn screening	• Informed consent
Protocol review	• Quality assurance studies do not require IRB	• IRB required unless use is routine laboratory quality assurance • Exception is court ordered uses
Other issues	• No markers remain for possible future uses—individual or population	• Concerns about privacy protections and confidentiality may arise

child or that are of importance to understanding a condition affecting children. If a state foresees the possibility that research using residual specimens will be done at a later date, a mechanism should be in place to inform parents of and obtain permission for that research. An up-front mechanism of informed consent, at the point of the heelstick, is one logical way of initiating the process of informed consent. Any research on identifiable samples that is not covered by the original consent would require recontacting the parents. Proposals to recontact patients with specific results should be justified to and approved by an oversight body before contact is made. Forensic (eg, for identification of a missing or deceased child) or clinical uses of the samples should be with the family's consent or with a legal mandate. If identifiable samples are maintained, policies and procedures need to be developed to define appropriate access for the purpose of forensic testing or other legal purposes (see Table 2).

Task Force Recommendations to Strengthen the Infrastructure for Surveillance and Research

The *Task Force* recommends that:

- State MCH programs should conduct a review of the newborn screening system and its relationship to the HRSA MCH Block Grant Performance Measures and evaluate the quality of data of the newborn screening-related performance measures.
- The federal HCFA should develop HEDIS measures to evaluate the health plans' performance within the newborn screening system.
- A federally-funded newborn screening research agenda should be outlined that aims to: develop better tests (more sensitive, more specific, and less costly); assess the validity and utility of new technologies (eg, tandem mass spectrometry, DNA-based testing, and other evolving technologies); and define appropriate uses of residual biologic samples for a population-based research and surveillance.
- The HRSA's MCHB should provide grants to states to stimulate development of newborn screening information systems that are connected to the medical home, with a focus on newborn screening system process and outcome evaluation, development of standardized datasets, analyses of cost-efficiency and effectiveness, and integration with other public health data systems. Support for technological innovation (ie, new test technologies) should include these measures.
- Pediatricians, pediatric subspecialists, and other health professionals who care for children should contribute to newborn screening data collection to advance knowledge about health outcomes and intervention effectiveness. Professional associations, the HRSA-funded National Newborn Screening and Genetics Resource Center, and state

newborn screening programs should develop strategies to assist health professionals in their efforts to participate in and learn from newborn screening information systems.

- Pilot studies should be undertaken to demonstrate the safety, effectiveness, validity, and clinical utility of tests for additional conditions and new testing modalities. Informed consent of parents is called for in all such pilot studies. These studies might be undertaken by individual states, regional or nationwide groups of states, or through federal grants provided to research institutions across the country.
- Federal and state public health agencies, in partnership with health professionals, families, and representatives of ethnic, minority, and other diverse communities, should:
 - Develop model legislation and/or regulation that articulates policies and procedures regarding utilization of unlinked and identifiable residual samples for research and public health surveillance. This process should include review and consideration of the recent recommendations to the President set forth by the NBAC for research involving human biological materials;
 - Develop model consent forms and informational materials for parental permission for retention and use of newborn screening samples;
 - Develop educational materials for parents that includes information regarding the storage and uses of residual samples;
 - Organize collaborative efforts to develop minimum standards for storage and database technology to facilitate appropriate storage of residual newborn screening blood samples at the state level; and
 - Consider creating a national or multi-state population-based specimen resource for research in which consent is obtained from the individuals from whom the tissue is obtained. Such a resource could be an alternative to retaining newborn screening samples for potential use in research.
- Using national recommendations, each state program should develop and implement policies and procedures for retention of residual newborn screening blood samples that articulate the rationale and objectives for storage, the intended duration of storage, whether storage is with or without identifiers, and guidelines for use of identifiable and unlinked samples. An advisory group for newborn screening programs with broad professional and family/community representation is a valuable resource in developing policies and procedures and in reviewing applications for use of retained samples. The advisory body also could determine priorities for use.

V. THE ECONOMICS OF SCREENING

Public health agencies should ensure adequate financing mechanisms to support a newborn screening program. Because states require universal newborn screening for certain conditions, they have an ethical and fiscal responsibility to ensure that children with identified disorders receive maximum benefit from early diagnosis and intervention. A newborn screening system is comprised of 5 parts: 1) screening, 2) short-term follow-up, 3) diagnosis, 4) treatment and management, and 5) program evaluation and quality assurance. Because financing is needed for each component, newborn screening systems need adequate funding to serve all children. Ensuring adequate finances, through public health spending and other funds, is essential.

Defining Cost Effectiveness

Screening is done to prevent disease and its consequences, with the expectation that expenditures now will reap benefits in the future. In making decisions about newborn screening systems, the value compared with the public cost has long been a consideration.^{33,40,81,100,195-197} In addition to having a reliable test and system that can benefit children, public health officials may be asked to justify the cost of population-based newborn screening.

Many believe that screening, as a tool for prevention, is a way to reduce costs.¹⁹⁸ However, screening may increase, not reduce, the cost of a public program. In addition, it may avert costs that otherwise would have been incurred within the health care system as a whole, or outside the health care system. Economists and health policy analysts use 2 types of calculations—cost benefit and cost-effectiveness—to estimate the potential for savings, potential for averting costs, and potential for achieving benefit in reduced mortality and morbidity.

Cost-benefit calculations attempt to value everything, including health effects, in terms of dollars.¹⁹⁸ The cost-benefit of newborn screening for particular conditions is the cost of screening and treatment minus costs averted in dollars.^{4,14,100,199} Although this makes it easier to perform comparisons, many object to the ideas that human lives and health can be represented by dollars. Also, there is disagreement about what monetary value to assign. Reaching agreement on the goal of the intervention (in this case screening) also is important—is the goal to save lives, prevent disability, reduce public medical expenditures, or something else?

Alternatively, cost-effectiveness analyses compare the cost of doing something to the cost of doing nothing, or of doing something else. It is useful in showing which alternative is preferable.¹⁹⁸

The Cost-Effectiveness of Newborn Screening

In 1988, the US Congress Office of Technology Assessment (OTA) published a review on the effectiveness and costs of newborn screening for specific conditions, compared with no screening.¹ This review was conducted using the best information available at that time, and was done using a “basic

approach” to newborn screening. The “basic approach” was common to all states, and was defined as collection and testing of a single blood specimen to identify cases of PKU and congenital hypothyroidism. Using the “basic approach”, the OTA analyses concluded that net health care savings per 100 000 infants screened (in 1986 dollars) was \$3.2 million, and that the net health care savings per case detected and treated was \$93 000.

The OTA also compared the cost-effectiveness of the “basic approach” to 6 expanded newborn screening strategies. These new strategies included variations that would test for additional diseases or conduct more intensive screening for PKU and congenital hypothyroidism. Unlike many previous efforts, these expanded strategies included the cost of specimen collection and follow-up. The OTA found that each of the expanded strategies for screening was more effective in detecting affected infants, and more costly than the “basic approach”. Based on their calculations, the OTA found that:

- detecting additional cases by adding tests to an initial (single) specimen is less costly than collecting and analyzing a second specimen, and
- more cases can be detected with repeat heelstick testing (which required a second blood specimen for additional tests or as follow-up to early discharge), but the cost of collecting additional specimens adds significantly to the overall cost.

The report states: “Each of the 6 expanded strategies would save more babies from deadly or disabling diseases than the basic strategy . . . but the incremental costs of achieving those extra successes are high.”¹ This was true whether additional specimens were collected to detect extra cases of PKU and congenital hypothyroidism, to detect homocystinuria, or as a precaution against missed cases. For example, the OTA found that the cost of detecting 1 extra case using an expanded 1-specimen strategy (testing for additional diseases from 1 sample) was about \$85 000. The OTA concluded that “this amount would buy an entire lifetime for a child with one of these disorders, and is low compared with the cost of many therapies currently considered accepted medical procedure.”¹

Notably, the OTA cost-effectiveness analysis did not include newborn screening for sickle cell anemia, biotinidase deficiency, congenital adrenal hyperplasia, as well as other conditions that were being screened for in some states and through pilot programs. Moreover, some believe that the OTA analysis did not fully take into account the public health or personal care burdens for identified conditions. If these factors were considered, the estimated net costs and savings would be different. For example, if additional screening tests could be performed using the original heelstick sample, without substantial increases in laboratory costs, the cost-effectiveness of newborn screening would be improved.

A critical step in conducting a cost-effectiveness analysis is determining what components are used to estimate the cost of screening. Often studies have

included only the cost of the screening itself, and not all 5 components of the newborn screening system.^{1,14,38,40,96,195,198,200,201} Additional elements that might be included, if the whole system were taken into consideration, are:

- In the screening component—the cost of informing families, obtaining a specimen, and laboratory analysis (including cases that prove to be false-positive);
- In follow-up and diagnosis—the cost of reporting and retrieving results, finding the family, performing a specialty diagnostic evaluation, and identifying the medical home; and
- In long-term management and treatment—the cost of multidisciplinary specialty services, special formulas and foods, durable medical equipment such as hearing aids, and ancillary services such as physical, occupational, or speech-language-hearing therapy.

Equally important to determine is a decision about which costs to include in the estimate of averted costs. For example, there are numerous financial implications associated with a chronically ill child within the context of a family. Unfortunately, because there are insufficient data on some conditions included in newborn screening programs, reliable estimates of averted costs related to these conditions cannot be made.

The OTA recommended that states continue to evaluate the effectiveness and cost-effectiveness of newborn screening programs as new tests become available; particularly the incremental effectiveness of incorporating new tests into various screening strategies (eg, single versus repeat sampling). They also concluded that the federal government “might put as a priority, the collection and evaluation of data that would allow careful analysis in [the] future of costs, as well as effectiveness of widespread screening for these disorders.”¹⁴ As the Human Genome Project moves from basic to applied science, and as this knowledge is incorporated into newborn screening programs, this type of federal investment should be given further consideration.

New Health System Economics: The Era of Managed Care and Integrated Delivery Systems

The health care system has changed dramatically over the past decade and has been shaped by concern about health care cost, and the growth of managed care and its associated changes in the health care delivery system.^{71,133,202} Public and private purchasing dollars have been consolidated, premiums and fees have been curtailed, and patients have been assigned to primary health care professionals/case managers who could act as gatekeepers. Newborn screening systems have been affected by these trends because they operate at the intersection of public health and medical care.^{65,71,72}

The Impact on the Health Care System

The most visible change in the health care system is the shift toward the purchase of managed care

arrangements, and a trend away from traditional indemnity insurance. A managed care organization is an agency through which services are purchased involving a network of health care professionals selected and overseen by the entity.⁷² Typically, the managed care plan (and often its network of providers) assumes financial risk. Managed care organizations have attempted to: 1) organize relationships between health care professionals, 2) limit what would be covered, and 3) control enrollee access to services.⁷² These specifications are defined in contracts between the purchaser and the managed care organization, as well as between the managed care organization and its network health care professionals.

Across the country, the transition of managed care has changed the structure and organization of medical practice. There has been: a shift away from inpatient care, a development of integrated health systems, a reorganization of health provider networks and relationships, a greater emphasis on accountability for cost and quality frequently through shared risk, and increased oversight from federal and state governments. Together, these trends have significantly affected the administrative side of physician practice.⁷¹ Physician and patient relationships have been affected and sometimes disrupted.²⁰³ Physicians have raised concerns about their ability to make referrals to appropriate specialists and subspecialists under third-party payer and managed care controls and restrictions.

The Impact on Public Health Agencies

In the wake of managed care developments, public health agencies and their population-based public health programs have faced fiscal and programmatic challenges. In fiscal terms, agencies with clinic-based services (eg, immunization, sexually transmitted disease testing) have experienced a loss of Medicaid patients and revenues when beneficiaries were assigned to a primary care health professional in private practice. With Medicaid buying managed care arrangements instead of fee-for-service care, the amount of Medicaid dollars available to support public health clinics is reduced.⁷²

However, each public health agency retains programmatic responsibility for population-based programs that protect the public's health.²⁰⁴ Despite decreased fiscal support, health departments have to consider the following:

- What functions and responsibilities must continue to be conducted by public health departments and how best are these public health activities financed?
- How should public health departments interact with managed care organizations and other third-party payers (eg, act as partner, service provider, or regulator)?
- What role should public health departments play in assisting managed care organizations and other third-party payers to integrate preventive medicine and health promotion into their products and services?

- What strategies lead to successful collaboration between public health and managed care organizations/third-party payers?

The Impact on Newborn Screening Programs

For newborn screening systems, public health departments continue to play an essential role in ensuring the service, including financing some aspects of the program with public dollars. For example, states may use tax dollars to supplement fees for newborn testing, to operate a state public health laboratory, to employ staff who do initial follow-up with physicians and families, and to finance treatment for uninsured or underinsured children.²⁰⁵ Public health agencies also have other responsibilities with costs attached, such as monitoring the quality of newborn screening laboratory services, ensuring the completeness of screening and follow-up, operating information systems, and protecting confidentiality and privacy.

In terms of testing, length of hospital stay for the newborn is an issue closely related to newborn screening and its costs. Before 1996, states reported that some newborn screening laws or regulations required repeat screening after early hospital discharge.^{6,206} In 1996, more than half of the states adopted new laws or regulations related to insurance coverage for newborns who are discharged early (typically defined as before 48 hours after a vaginal birth and 96 hours after a cesarean birth), partially in response to concerns about the reliability of newborn screening tests based on samples collected from infants aged 24 hours or less.^{116,207-210} Many of these new laws required that health plans cover 1 or more newborn visits (in the home or clinical setting) subsequent to early hospital discharge that must include collection of an adequate sample for newborn screening (eg, Indiana, Kentucky, Missouri, New Hampshire) or "medically necessary and appropriate tests." When appropriately implemented, these laws provided for additional payments to cover the cost of repeat testing.

However, repeat testing costs are only one small component of a newborn screening system. As with other population-based public health services that have a medical care component, third-party insurance purchasers and managed care organizations may not recognize the importance of third-party payment for the newborn screening system. Newborn screening services are an accepted and essential component of pediatric care, and should be a service covered and delivered by any third-party payer. Managed care organizations and other third-party payers have a role to play in all parts of newborn screening, including testing, initial follow-up, diagnosis, and management through long-term treatment and follow-up. For example, testing fees may be included in the hospital costs or be a separate cost for a newborn, and the cost of retrieving and reporting newborn screening test results are a part of the cost of initial visits to primary care health professionals. There is little evidence that managed care organizations or other third-party payers have been actively

involved in newborn screening systems. This is an area for further study and improvement.

Maintaining the quality of newborn screening systems amid these changes requires the commitment of public health agencies, health professionals, and managed care organizations/third-party payers. Each third-party payer or managed care organization must have the responsibility to ensure that these services are readily available in the network or by referral to health care professionals and facilities outside the network.²¹¹ Some diagnostic and treatment services needed for follow-up of newborn screening require both expertise available only through a pediatric specialist or subspecialist, and the ongoing comprehensive care that these subspecialists provide. In some cases, appropriate services will only be obtainable outside the third-party payer network through health care professionals or facilities with teams of professionals who specialize in a particular condition. For example, diagnostic services and design of a plan of care might best be achieved through a center of excellence or subspecialty center that has expertise in sickle cell disease, metabolic conditions, or speech-language-hearing treatment of the very young child.

Financing Newborn Screening Systems

States fund newborn screening programs in different ways. Most states set and collect fees for newborn screening tests. However, fees alone are not adequate to finance a newborn screening system, and public health funding is often used to supplement these fees.

Fees for Newborn Screening

States report use of the following funding strategies for newborn screening programs (based on 1996 information submitted by the states to the CORN)⁶:

- Most states billed patients, health care professionals, hospitals, or third-party payers a newborn screening fee. Some states reported no billing and used only public dollars. Eight relied on state general funds (Georgia, Indiana, Kansas, Maryland, New York, North Carolina, Texas, and Wyoming) and 6 used federal grants (Georgia, Kansas, Maryland, New York, Pennsylvania, and Texas).
- Among the 23 states that provided data, the fees charged per newborn ranged from approximately \$40 in Delaware and Massachusetts to less than \$15 in Kentucky, Minnesota, and New Hampshire. These variations reflect both the number of disorders states choose to screen for and the different levels of services supported by newborn screening fees.

A survey on state fees in 1992 showed similar findings, including the following:

- Forty states had set fees for newborn screening and collected them.
- In 21 of the 40 states that charged fees, the laboratory was responsible for fee collection.
- The testing fee included both laboratory and other program services in 30 states. Of these states, 17

financed more comprehensive services including some follow-up and treatment costs.

- While 17 states placed fees into a fund designated for newborn screening program support (and 8 into a special laboratory fund), 10 states returned collected fees back to general revenue budget funds.

Experience of the MCHB technical assistance team to state newborn screening programs indicate additional costs to consumers or their insurers. These include hospital fees that may be sizeable (\$100 in some hospitals) for heelstick blood collection.

Programs Designed for CSHCN

Title V of the Social Security Act mandates that each state put in place community-based, family-centered, culturally competent, coordinated systems of care for CSHCN. Healthy People 2000 called for implementation of these comprehensive systems in all states by the year 2000.

Much has been achieved in establishing these systems, but much remains to be done to accomplish full implementation for all CSHCN. These are defined as “those who have or are at increased risk for a chronic physical, developmental, behavioral, or emotional condition and who also require services of a type or amount beyond that required by children generally.”²¹² Healthy People 2010 reiterates the establishments of these comprehensive community-based systems as a goal, and the HRSA’s MCHB is working actively with the states and other partners to make that goal a reality within the next 10 years.

The federal Supplemental Security Income (SSI) program provides income support and Medicaid coverage to children with disabilities. However, the eligibility definitions of the program have been changed several times in recent years through modifications in federal law or regulation. The result is that families and health care professionals may be confused about the status of children with certain conditions. In addition, reports from pediatric subspecialists suggest that some SSI guidelines for conditions such as sickle cell disease (which is included in state newborn screening programs) do not fit with accepted professional views on the severity of the disease.²¹³

All states have early intervention programs for infants and toddlers, with some covering children diagnosed with certain conditions and others including children “at-risk.” These early intervention programs are administered by a variety of state agencies; one-third are administered by MCH Title V programs. Similar to special education programs, federal rules require states to identify and serve eligible children. Many children with genetic conditions are included in these programs. State education, Medicaid, and public health agencies have administrative and fiscal responsibility for these services.

Health Care Coverage

Health coverage costs are a significant budget and policy issue in every state. Children’s health cover-

age is of particular importance to states, with over one-third of all US births being financed by Medicaid and, in most states, more than half of children using Medicaid or the State Children’s Health Insurance Programs (SCHIP). States have regulatory authority over many insurance practices, both in the public and private sectors. In other words, state actions have substantial influence over whether children with conditions identified through newborn screening have health coverage and how adequate that coverage will be to meet their care and treatment needs.

Private insurance. For children covered by insurance, the Health Insurance Portability and Accountability Act (HIPAA, also known as the Kassebaum-Kennedy legislation) offers protection for newborns in every state.^{214,215} The HIPAA prohibits preexisting condition exclusions for babies if their mother is covered (whether covered by private insurance or Medicaid), and if the infant is enrolled in the plan during the first 60 days of life. In addition, when coverage starts in infancy, the HIPAA provides that prohibitions on preexisting condition exclusions can be effective throughout childhood and beyond. This HIPAA provision was designed specifically to protect infants with genetic, chronic, and other disabling conditions that formerly were considered “preexisting conditions” under many private health plans. However, because states had to conform to many larger provisions of the HIPAA, infant coverage has not been successfully discussed and actively enforced.

States can mandate that benefit packages of private health insurance products include items such as special formula or nutrition supplements. Several states have adopted such mandates. However, because of the Employee Retirement and Income Security Act (ERISA), states’ mandates do not affect employer-based benefit plans that are self-funded (also known as “self-insured”).²¹⁶ As a result, as many as 25% to 50% of those covered under private employer-based plans are estimated to not be protected by the requirements of state insurance benefit mandates.

States have used regulatory authority to direct other types of health plan practices beyond benefits. In terms of managed care, states have adopted a variety of regulations, including some approaches that could be modified to protect CSHCN. For example, by late 1997, 22 states had enacted laws requiring that health plans permit direct access to a particular type of specialist. However, none of these laws specifically addressed direct access to specialty care for children with chronic or disabling conditions. In 18 states, each health plan is required to establish a procedure by which an enrollee may secure a standing referral to a specialist. CSHCN would benefit from this type of protection.

Medicaid. Medicaid is an important source of coverage for children with conditions identified through newborn screening. Medicaid finances an estimated 40% of births, and these infants are automatically eligible as newborns and remain eligible throughout the first year of life. Although federal Medicaid law

requires states to implement automatic newborn eligibility rules and guaranteed coverage for the first 12 months of life, many states do not have effective procedures to implement these guarantees. Medicaid also has a comprehensive benefit package, known as the Early and Periodic Screening, Diagnosis, and Treatment (EPSDT) program. Through the EPSDT program, Medicaid requires that states provide coverage and financing for a wide range of care and services that are medically necessary for CSHCN; including formulas, hearing aids, and therapies needed by children with conditions identified through newborn screening.

Since 1993, most state Medicaid programs have moved toward the purchase of managed care coverage for beneficiaries.⁷² Although few managed care plans have had previous experience providing services to CSHCN, studies suggest that managed care decreases the utilization of specialists by children. One study of Medicaid managed care contracts recommended that state Medicaid contracts: clarify pediatric benefits, define capacity requirements of health care professionals, develop a medical necessity standard specific to children, identify pediatric quality-of-care measures, set pediatric capitation rates, and create incentives for quality in pediatric care.²¹⁷

SCHIP. For low-income children who are not privately insured and not eligible for Medicaid, Congress enacted Title XXI of the Social Security Act, which established the SCHIP in 1997.²¹⁸ Under this program, states are given grants to subsidize health coverage for these children. States may choose to purchase coverage through Medicaid or private insurance (and in some cases directly purchase services from health care professionals). Each state can establish its own guidelines for eligibility based on income, age, disability status, and so forth. If not using Medicaid, states also determine what benefits will be covered under the SCHIP plans. A recent review of the benefit packages of non-Medicaid SCHIP plans found that 5 states do not cover hearing aids, durable medical equipment, and other devices; and that coverage for therapies is uneven with exclusions of developmental conditions or chronic conditions not expected to improve.²¹⁹

Goals for States' Financing of Newborn Screening Systems

In discussions regarding the financing of newborn screening systems, the Task Force identified 3 distinct goals:

- *Adequate financing for screening, short-term follow-up, and diagnosis.* The screening, follow-up, and diagnosis components of the system are generally funded by some combination of newborn screening fees and public dollars. Many states cover most or all of the costs for testing with newborn screening fees; some states supplement or cover screening test costs through general public health funding. Sufficient funds from fees and/or public funds are not always available, however, to ensure adequate short-term follow-up and diagnostic testing. Reliance on third-party payers for short-

term follow-up and for diagnostic testing and interpretation is problematic, in part because these activities need to be conducted expeditiously and because the health insurance status of newborns is often uncertain.

- *Adequate financing for comprehensive care and treatment of all individuals with conditions identified through newborn screening.* Funding for comprehensive medical care and treatment is challenging, and treatment of some conditions identified through newborn screening is costly. Not all children have health coverage or the means to purchase needed treatment. Managed care plans and other third-party payers often do not cover items such as special formulas, special foods, neurodevelopmental assessments, and therapies. Important psychosocial services and other support services for families are also less likely to be funded through health plans. Many managed care plans restrict access to specialized services or require that in-network health professionals who lack appropriate expertise deliver care. For children with complex conditions, treatment may best be delivered by a multidisciplinary team with specialized expertise; however, development and support of such teams requires financing beyond that provided through any form of insurance. Thus, many children with the disorders identified by neonatal screening do not receive optimal care because they have inadequate insurance coverage and/or lack access to qualified health professionals. For many, the situation is exacerbated when they reach adulthood and no longer qualify for public programs such as Medicaid, the SCHIP, and Title V-funded programs for CSHCN.
- *Adequate financing for program evaluation and quality assurance.* Public health agencies and newborn screening program staff are essential to the success of newborn screening systems through their role in activities to ensure laboratory quality, outreach and tracking of families, long-term follow-up, and so forth. State public health agencies and their newborn screening program units should interact with and ensure the quality of all parts of the newborn screening system. Currently, most states do not provide financing for outcomes data collection and evaluation, and this limits their ability to improve the system and to evaluate cost-effectiveness.

Task Force Recommendations to Improve Financing of Newborn Screening Systems

- States should assure adequate financing of all parts of the newborn screening system: screening, short-term follow up, diagnostic testing, comprehensive medical care/treatment, and evaluation of the system. If newborn screening fees are not adequate, funding of all components of the system could be accomplished with other public health dollars or by third-party payers. Other uses of newborn screening fees should not be considered until all of the components of the newborn screening system are fully funded.

- States should take responsibility for blending resources available through Title XIX (Medicaid), Title V (MCH Block Grant), Title XXI (SCHIP), and private insurance to guarantee necessary coverage and financing for all children and adolescents with a condition diagnosed through the newborn screening system.
- State contracts for publicly-subsidized third-party insurance plans that cover children (eg, Medicaid and SCHIP) should explicitly require coverage for newborn screening and those services, including management and treatment, related to disorders identified by newborn screening. State contracts should require that third-party payers ensure access to health care professionals with appropriate pediatric expertise within the network or through out-of-network referrals.
- States, in cooperation with health professionals and payers, should put mechanisms in place to identify the third-party payers for newborns immediately following birth. For example, all states should operationalize the automatic newborn eligibility requirements under Medicaid and the HIPAA newborn coverage provisions that require infant coverage and prohibit preexisting condition exclusions for newborns.
- Purchasers—public and private—should ensure that the benefits packages they pay for includes the care and services defined by the AAP Scope of Health Care Benefits Statement and the CORN guidelines.^{9,143}
- In the SSI program, the federal government should review the technical appropriateness of guidelines, and evaluate the consistency of their application, for children with conditions identified through newborn screening.

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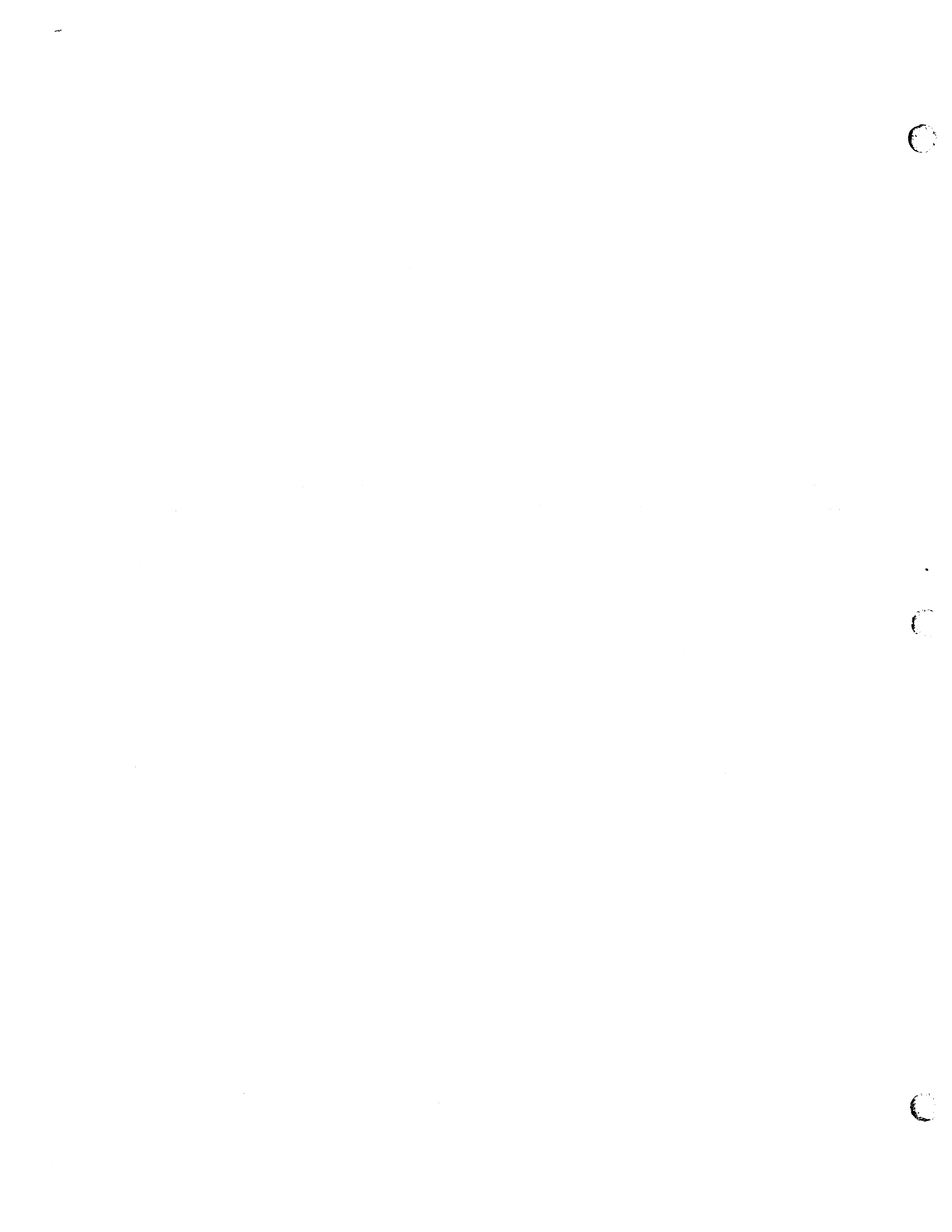
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APPENDIX C

**Scientific Article
Newborn Screening in Delaware
Delaware Medical Journal,
published by the Medical Society of Delaware,
Volume 75, May 2003, Number 5**

Newborn Screening in Delaware

Louis E. Bartoshesky, M.D., M.P.H.

Abstract: *Newborn screening for metabolic, hematologic, and endocrinologic disorders is a well-established public health function. Recent technological advances have made screening possible for more disorders. For many of these disorders, there is evidence that screening is effective; however, some of these disorders are rare, and their response to therapy and their natural history are not completely understood. A number of states have instituted "expanded" newborn screening utilizing a combination of established and new technologies. Other states, including Delaware, have studied the experiences of the states doing expanded screening and have decided to proceed with expanded screening as well. Since early 2003, Delaware has been screening newborns for about 25 disorders, including amino acidopathies, organic acidurias, fatty acid oxidation disorders, hemoglobinopathies, and endocrinopathies.*

INTRODUCTION

Newborn screening is a public health program aimed at early identification of conditions for which early and timely intervention can lead to the elimination or reduction of associated mortality, morbidity, and disability.¹ Newborn screening is a program, not just a test. It includes: 1) screening – the testing of the newborn; 2) follow-up – rapid location and referral of the infant whose screen is positive; 3) diagnosis – definitively confirming or excluding the disorder for which the screen was positive; 4) management – rapid implementation of needed therapy; and 5) evaluation – validation of procedures and education of professionals and the public.

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HISTORY

Robert Guthrie introduced newborn screening in the early 1960s.¹ He devised a technique for measurement (a bacterial inhibition assay) of the amino acid phenylalanine on a small spot of blood collected from an infant's heel onto a small piece of filter paper. Phenylalanine is elevated in the blood of children with phenylketonuria (PKU). Guthrie proposed that early identification of affected children followed by appropriate dietary management could prevent the moderate to severe mental retardation characteristic of children with untreated PKU. His proposal was quickly accepted. Prevention of mental retardation was a popular concept in the 1960s. In 1963, Massachusetts established a program of mandated screening of newborns for PKU. Various (but not all) public health, medical, and child care organizations, newspapers, magazines, and consumer groups supported screening, and by 1975, 43 states had laws requiring screening, and all states were screening new-

borns for PKU. In subsequent years, further tests were added to the newborn screening programs in various states. It has been argued^{1,2} that, in retrospect, the enthusiastic adoption of universal PKU screening may have been too hasty. Knowledge regarding PKU, its clinical variability, the validity of the screening tests, the prognosis with treatment, and the difficulty of the treatment were rudimentary when the PKU screening programs were launched. Validation of the screening test, confirmation of the safety and effectiveness of the treatment, and understanding of the disorder all came well after the screening had been institutionalized. It turned out, fortunately, that diagnosis and treatment of PKU was reliable and effective. According to Paul, "The history of PKU shows that it is easy to exaggerate the ease and efficacy of treatment and to underestimate the cost."²

NEWBORN SCREENING PROGRAMS

Newborn screening programs vary from state to state. The variations reflect differences in state political and economic environments, public health technical capabilities, and demographic factors.^{3,4} Some states, as of 1997, were screening for three disorders; others for as many as ten. As of 1997, two states required active parental consent for newborn screening, while the rest screened on the basis of "informed non dissent." (That is, a state's public health department assumes that informed parents would want their infant to have the benefit of screening, so lack of dissent is implied to mean consent.) Some states utilized advisory boards, which included consumers, while others depended on scientific review boards to help them decide for which disorders to screen. In some states, screening policies were made on an extemporaneous basis by Public Health Departments and were not based on professional or public consensus.⁵

Ideally, a screening test should be instituted as a public health tool only if it has been demonstrated to be of value in well-controlled pilot studies. The screening test should be simple, safe, and inexpensive, with acceptable sensitivity, specificity, and predictive value. The disorder tested for should be common enough to merit the effort, and there should be adequate re-

sources available for confirmation and treatment. The test should be proposed by public health officials to an appropriate review or advisory committee for consideration. The process should be careful and deliberate.^{1,6,7} There should be consumer involvement in the process^{1,6,7} because consumers ultimately bear the fiscal responsibility for public health programs and because, in a democracy, individuals expect to have a voice in policy decisions that have implications for their health and welfare.⁵

Holtzman, a consistent advocate for a position not shared by most newborn screening professionals,⁸ has argued that only for PKU, congenital hypothyroidism, and perhaps sickle cell disease has there been systematically collected evidence for validity and utility based on the criteria cited above. As of 1997, all states screened for PKU and congenital hypothyroidism, and 45 screened for sickle cell disease. The other disorders then screened for in the various states, according to Holtzman,^{8,9} failed in some way to meet all of the proposed criteria.

A NEW TECHNOLOGY

In the early 1990s, tandem mass spectrometry (conventionally abbreviated as MS/MS) was proposed as a method that could be of value in newborn screening. The technology was shown to be able to measure 25 or more metabolites from a blood spot in about two minutes. It could detect levels of amino acids (including phenylalanine) and acyl carnitine derivatives of organic acids and fatty acids.¹⁰⁻¹² It was proposed that measurement of these metabolites would make it possible to screen for 30 or more inborn errors of metabolism. (For details on the technology, please see Millington reference 11).

At various regional and national meetings through the mid 1990s, newborn screening professionals cautiously discussed MS/MS and its promise as a tool for screening newborns. An expert work group convened in 2000 and published recommendations on MS/MS and newborn screening.¹⁰ The work group described a number of technical concerns and questioned whether there was adequate information on many of the metabolic disorders to make them appropriate candidates for screening. According

to the work group, "Additional research is needed to determine which interventions work for MS/MS detectable disorders."¹⁰ Some disorders are likely to be clinically heterogeneous, with some apparently affected infants likely to require intervention and others not¹³; other disorders are so rare that there is little clinical data on them; and still others are so severe that early detection might be of no clinical value. The work group did recommend that states consider adopting MS/MS for what has come to be called "expanded newborn screening." (By the time of publication of the work group's report in April 2001, four states had already begun expanded screening using MS/MS.) The work group warned that technical difficulties should be anticipated. It suggested national collaboration to allow for study of the disorders and urged that in each state the public should receive accurate information regarding expanded newborn screening and the evolving knowledge regarding its strengths and weaknesses. They noted that at least one disorder (medium chain acyl CoA dehydrogenase [MCAD] deficiency) that can be screened for only by MS/MS was likely common enough, severe enough, and responsive enough to relatively simple intervention that states should add MCAD deficiency to their list of disorders for which they screen.¹⁰

PUBLIC DISCOURSE

Before the work group had published its report in 2001, there had been numerous magazine articles, newspaper stories, television reports (including a segment of an episode of the popular television show "ER"), and Internet sites discussing expanded newborn screening.¹⁴⁻¹⁹ Typically the stories told, often movingly, of a family who had a child die or develop a substantial disability from a disorder that could have been identified by an expanded screen. Some articles were carefully constructed and considered the various aspects of expanded screening.¹⁹ Others were more spectacular, such as "Parents Suing Doylestown Hospital" in the *Philadelphia Inquirer* on March 22, 2000.¹⁸ This article reported that the hospital had not elected to adopt expanded screening (which is optional by hospitals in Pennsylvania), and a child was born

there who eventually was diagnosed with propionic acidemia, a disorder of organic acid metabolism. The child had an episode of extreme metabolic acidosis, and as a consequence was left with severe developmental disabilities. The parents contended that if the hospital had adopted expanded screening, the condition would have been diagnosed, and with complex interventions, including a change in diet, the disability could have been prevented.²⁰ A few months later (May 27, 2000), the *Inquirer* carried the headline "After Suit Hospitals Expanding Baby Tests."

On the CBS Evening News¹⁷ the case was of an eight-month-old who died, apparently of Sudden Infant Death Syndrome (SIDS), but was later proved to have had MCAD deficiency. On the World Wide Web, there was a site (www.tylerforlife.com) dedicated to Tyler, a newborn who died in Pennsylvania with galactosemia prior to Pennsylvania's adopting screening for that disorder.¹⁶ (Galactosemia is not detected by MS/MS.) The site passionately urges parents to encourage, even threaten, states to adopt expanded screening. In some of these popular publications and productions, the cost of expanded newborn screening is reported as being \$25. Some articles have acknowledged that \$25 is only the cost of the test and does not include increased follow-up costs, increased state infrastructure costs, and increased costs of evaluation and testing to confirm or rule out diagnoses suggested by the screening. Increasing the number of disorders screened for necessarily results in cost increases well above \$25 per baby. Furthermore, the articles generally failed to note that the annual increased cost of expanded screening to a state would actually be about \$25 multiplied by the number of babies born in a state per year.

DECISION IN DELAWARE

As of January 2000, Delaware screened for four disorders (PKU, congenital hypothyroidism, galactosemia, and sickle cell disease). Since 1999, laboratory testing has been done at the Delaware Public Health Laboratory in Smyrna. Prior to 1999, Delaware had contracted with another state for newborn screening laboratory services and screened for six disorders. When the labora-

tory component of screening was moved in-state, it was decided to simplify and initially to screen for four disorders (the fifth was added in late 2001) and consider expansion after the program had become well-established in-state. Those decisions were made within the Division of Public Health as required by state regulation.²¹ There had been a Delaware genetics and newborn screening advisory committee, but it had dissolved in the early 1990s. In 1999, the Newborn Screening and Infant Formula Fund Advisory Committee (hereafter referred to as "the committee") was reestablished as the newborn screening program looked for assistance in deciding how to deal with the issues of expanded screening. The value of an advisory committee for the Delaware program was stressed by the National Newborn Screening Resource Center, which had reviewed the Delaware program in 1993 and 2000.²² The Delaware volunteer advisory committee includes several parents of children with metabolic disorders, an attorney, an ethicist, a university biologist, several physicians, a nurse, and a number of representatives from state agencies, including Public Health, the Office of the Insurance Commissioner, and Medicaid.

In 2000, the Newborn Screening Program (NSP) personnel and the director of the State Laboratory proposed to the advisory committee that Delaware add a test to its newborn screening battery, specifically measurement of 17 hydroxy progesterone, a hormone elevated in the blood of children with the most common form of congenital adrenal hyperplasia (CAH). The NSP staff described the disorder to the committee, outlined the testing, described how follow-up would be accomplished, and reported the potential benefits and shortcomings of the test. There are false positives; the disorder is readily diagnosed clinically (i.e., without screening) at birth in most affected females who have ambiguous genitalia; and there is clinical heterogeneity resulting in some children being identified as affected who may need no intervention or would not need intervention until adulthood. The disorder is relatively common and may be life threatening, particularly in boys, if not detected early. Cost benefit studies done in states that have been screening for CAH for some time suggested a favorable ratio of dollars spent to

dollars saved.²³ The advisory committee suggested that the NSP add the test, aware that it might not strictly meet the criteria outlined by Holtzman^{8,9} and others,²⁴ but convinced that it had been of value in other states and would be of benefit, at a reasonable cost, to the babies of Delaware.

In late 2000, the NSP brought expanded newborn screening to the advisory committee for review. Some committee members were already aware of MS/MS and expanded screening. At least one member of the advisory committee was aware of a letter that had been received by the CEOs of each of the hospitals in Delaware at which babies are delivered. The letter, from a Pennsylvania mother of a child with a metabolic disorder, strongly urged that the hospitals adopt expanded screening and warned of possible future lawsuits if the hospitals did not.

The NSP staff described the expected increased cost of screening if MS/MS technology were adopted: an increase from \$40 per baby to about \$60 per baby. The NSP staff reviewed the principles to be considered when deciding about adding a new test^{1,8,9,11-13,21} and pointed out MS/MS potential shortcomings and benefits as they had been outlined by the MS/MS work group.¹⁰

The NSP staff reviewed for the advisory committee the retrospective discussions on the rapid adoption of PKU screening in the 1960s.² The staff informed the committee of several inquiries from state legislators regarding expanded screening. Information available to the public was reviewed.¹⁴⁻¹⁹ The difficult issue of mandatory versus voluntary screening was raised. The committee seemed to agree, but was not unanimous, that active informed consent might be waived if "clinical validity and utility have been established and parents are provided sufficient information to understand the reasons for screening."⁸ The Massachusetts experience was reviewed with the Delaware advisory committee.²⁵

Massachusetts began expanded screening in early 1999 following a lengthy consideration. The Massachusetts Department of Public Health (DPH) convened a special committee in 1997 to assist in deciding about expansion. After much deliberation and consultation with parents, other consumers, and experts in metabolic disease, medical ethics, public health, and medical eco-

nomics, the Massachusetts committee advised its DPH to expand screening. They suggested that there was adequate evidence to make screening for ten disorders mandatory. The Massachusetts committee suggested that the Massachusetts DPH offer screening for 20 other disorders, but since information on those disorders was judged to be incomplete, specific parental consent should be sought before a baby is screened for those 20. Massachusetts has devised a consent system consistent with the recommendations of its advisory committee and since 1999 has been screening for 30 disorders, ten mandatory and 20 requiring a consent.^{25,26} Other states have offered expanded screening under the same consent procedures in place prior to expanded screening.

By mid 2000, Pennsylvania was already offering expanded screening with MS/MS, New Jersey and New York had announced they would be expanding within the year, and Maryland was conducting discussions with its advisory committee and its legislature about expanding its screening program. MS/MS newborn screening would soon be the "standard of care" in the Middle Atlantic States.

The advisory committee suggested that the Delaware NSP proceed with establishing expanded screening. It suggested initiating MCAD deficiency screening as soon as possible and adding amino acid, organic acid, and fatty acid oxidation screening as soon as the equipment could be standardized and as soon as the NSP staff could be expanded to meet the projected increased workload. The recommendation was reviewed with the director of the Division of Public Health, according to Delaware regulations,²¹ who approved expansion. MS/MS equipment was acquired, necessary staff was added in the laboratory and in the follow-up office, and old and new staff attended appropriate education programs so they could be comfortable working with MS/MS technology.

While the laboratory staff prepared to begin expanded screening, the follow-up and medical staffs prepared an updated parent brochure with information on disorders to be screened for and circulated it to obstetricians' offices, birth hospitals, and pregnancy education programs. The Practitioner's Manual, first produced in 1995 as a guide for primary care physicians,

was also updated. It includes detailed discussions of the disorders screened for, techniques of screening, and an outline of proper follow-up of infants who are screened as "positive." The manual has been circulated to pediatricians, family physicians, pediatric nurse practitioners, neonatologists, neighborhood health centers, birth hospitals, and obstetricians.

NEWBORN SCREENING IN 2002 AND BEYOND

By late 2002, many more states had adopted expanded screening using MS/MS technology. Some had decided to add only MCAD deficiency screening; others had elected to screen for 25 or more disorders. There continues to be discussion about what is most appropriate. Some authorities are convinced that expanded screening is cost-effective, ethically and scientifically sound, and an essential public health activity.²⁵⁻³¹ MS/MS is reported in these and other studies to be sensitive, reasonably specific, cost-effective, and to have an acceptable predictive value. According to Filiano et al., expanded screening will bring "diminished morbidity and large savings in chronic care and critical care costs."³² They believe MS/MS meets "current guidelines for screening tests," and that MS/MS 1) can identify disorders that are well-defined clinically and biochemically; 2) is sensitive enough and has acceptably few false positives; 3) screens for conditions with "collectively" a known and significant incidence; 4) screens for conditions in which early diagnosis and intervention will prevent or diminish morbidity and mortality; 5) will assist in genetic counseling; 6) has costs that are small compared to treating late diagnosed children; and 7) is safe.³²

Others are concerned about heterogeneity in the disorders, fearing some children may receive unnecessary evaluations and treatments and be incorrectly labeled as "diseased."^{13,33,34} Pollitt is skeptical of the cost/benefit studies, wonders what should be considered acceptable specificity and predictive values, and questions the benefit of screening for very rare, possibly untreatable disorders.³⁵ Holtzman for some time has been concerned about appropriate consent for newborn screening, and his concerns are

magnified with expansion of screening.^{3,6,8,9} Leonard, in the United Kingdom, is concerned that "...once again a screening technology looks set to be driven by enthusiasm and opinion rather than evidence."³⁶ Virtually all 50 states disagree and have begun or are planning to begin expanded screening. Two recent American cost/benefit studies are strongly supportive of expanded newborn screening.^{30,31}

CONDITIONS SCREENED FOR IN DELAWARE

Phenylketonuria (PKU) is an autosomal recessive disorder. Children with PKU have a deficiency or absence of the enzyme phenylalanine hydroxylase. Untreated PKU is associated with moderate to severe mental retardation and seizures. Treatment, which sounds simple but is not, is a diet low in phenylalanine probably best continued for life. Outcome is excellent in children identified and treated in the first few weeks of life. There is clinical and laboratory variability among affected children. Screening had been by chemical or bacterial inhibition techniques but is now done by MS/MS. All states and many countries on all continents screen for PKU.

Congenital hypothyroidism (CH) is deficiency of thyroid hormone. It is etiologically heterogeneous. Early diagnosis and treatment with thyroid hormone prevents the mental retardation associated with diagnosis made after a few weeks of age. All states screen for CH. MS/MS technology is not involved in CH screening. Several studies in the United States and elsewhere have shown screening for CH and PKU to be cost-effective.^{37,38}

Galactosemia is an autosomal recessive deficiency of the enzyme galactose-1-phosphate uridyl transferase (GALT), which catalyzes conversion of galactose-1-phosphate to glucose-1-phosphate. Screening involves estimating levels of GALT and total galactose. Affected, untreated children are prone to septicemia in the first few weeks of life and invariably develop neonatal liver disease, renal disease, cataracts, early ovarian failure, slow growth, and mental retardation. Early diagnosis and treatment prevent most of the medical complications (short stature and ovarian failure appear to be exceptions). Developmental outcome in treated children is

good, but there is evidence that even some adequately treated children have language delay and are at risk for learning disabilities. Treatment is avoidance of galactose-containing food. There are variant forms, clinically mild or insignificant, which need to be distinguished by definitive testing.²⁰ Almost all states screen for galactosemia. MS/MS techniques are currently not used in galactosemia screening, though MS/MS may eventually be adapted to measure galactose.

Congenital adrenal hyperplasia includes a number of inherited disorders of synthesis of adrenal cortical hormones. Newborn blood specimens are screened for levels of 17 hydroxyprogesterone (17 OHP), which is elevated in children with 21-hydroxylase deficiency, the most common of the congenital adrenal hyperplasias. The severe deficiency presents as ambiguous genitalia in the female and as electrolyte imbalance, hypoglycemia, vomiting, and shock in the male and in some virilized females who were mistaken for males at birth. Treatment is replacement of missing adrenal hormones. Outcome is generally excellent. It may be difficult in the newborn period to distinguish the children who are at risk for electrolyte imbalance ("salt wasters") from children with less serious forms of 21-hydroxylase deficiency.²⁰ Assay of 17 OHP levels does not currently involve MS/MS. MS/MS can be adapted to estimate levels of 17 OHP as well as various adrenal hormones such as cortisone and aldosterone. It is likely that in the future many states will make such adaptations and be able to make more precise identification of the various forms of CAH utilizing MS/MS.³⁹

Sickle cell anemia is one of a number of hemoglobinopathies that can be identified on newborn screening. Early diagnosis of sickle cell anemia, done by hemoglobin electrophoresis (not MS/MS), allows for early family education about the disorder and early administration of prophylactic antibiotics, which has been shown to substantially reduce mortality in the early years of life.²⁰ Almost all states screen for sickle cell disease.

Biotinidase is an enzyme involved in cellular recycling of the vitamin biotin. Screening involves a fluorescent method of identifying the presence of the enzyme. Deficiency may result

in seizures, hearing loss, developmental delay, and rash. Treatment is with high doses of biotin with good outcome.²⁰ MS/MS is not used.

Medium chain acyl CoA dehydrogenase (MCAD) deficiency is the most common (1/15,000 live births) of the autosomal recessive disorders of fatty acid oxidation (FAO). Screening is based on estimation (by MS/MS) of the acyl carnitine derivatives of the several fatty acids. Clinical manifestations of MCAD deficiency and other FAO disorders are variable but may include hypoglycemia, hypotonia, seizures, developmental delay, intermittent vomiting, cardiomyopathy, a Reye syndrome-like picture, and even sudden death. Treatment is avoidance of fasting, vigorous nutritional support during times of intercurrent illness, diet low in long chain fatty acids, and sometimes treatment with carnitine or other medications. Confirmation of diagnosis may be difficult. Screening after a few weeks of age may not be reliable. Outcome in appropriately managed MCAD deficiency is believed to be very good, but the apparent clinical variability of MCAD and particularly of the other less common FAO disorders (abbreviated as GA II, SCAD, LCAD, LCHAD, VLCAD, and CPT) makes precise prediction about outcome difficult.²⁰

The organic acidurias are a group of inherited (autosomal recessive) disorders of metabolism characterized by accumulation of one or more organic acids in blood, urine, and cerebrospinal fluid (CSF). Screening is by estimation of acyl carnitine derivatives of the various organic acids by MS/MS. Clinical presentations are variable, but often include vomiting, lethargy, seizures, failure to thrive, pre-disposition to septicemia, coma with hypoglycemia, acidosis, and often ketosis. Among the organic acidurias screened for are glutaric aciduria I, methylmalonic aciduria, propionic acidemia, isovaleric acidemia, B-ketothiolase deficiency, HMG lyase deficiency, and B-methyl crotonyl carboxylase deficiency. Treatment of the organic acidurias may be difficult and not always successful but includes specialized diet, avoidance of fasting, and sometimes medications such as carnitine.²⁰ All of these are rare with cumulative frequency of about 1/15,000.

Concentration of some amino acids can be estimated by MS/MS permitting screening for PKU, tyrosinemia, argininemia, citrullinemia, homocystinuria (elevated blood methionine), and maple syrup urine disease (characterized by elevated branched chain amino acids leucine, isoleucine, and valine). As is true of virtually all metabolic disorders, there is variability in presentation and outcome. Treatment of these disorders is complex and outcome variable, even with early diagnosis and intervention.²⁰

Children with galactosemia, biotinidase deficiency, organic acidurias, FAO disorders, and amino acidopathies including PKU should be referred to metabolic centers; children with hemoglobinopathies, to pediatric hematologists; and children with endocrinopathies, to pediatric endocrinologists.

CONCLUSION

Newborn screening for metabolic, hematologic, and endocrinologic disorders is a well-established public health program. The recent adaptation of tandem mass spectrometry (MS/MS) to newborn screening has made screening possible for many disorders. Newborn screening is likely to continue to change. In time, some disorders may be dropped from programs and new ones added (e.g., several states screen for cystic fibrosis; some still do not screen for galactosemia).

New technologies and new adaptations of older technologies will likely soon make further extensive expansion possible (for example, techniques utilizing DNA technologies). There are indications that MS/MS could be adapted to screen for lysosomal disorders such as Tay-Sachs disease, and for disorders of glycosylation – the latter a group of disorders only recently identified.^{20,41} Already, several states are using DNA technology to perform “secondary screening” to promptly confirm and clarify screening results. For example, these laboratories have the ability to identify the presence of the most common MCAD mutations on a fraction of the blood spot from infants who screened positive for MCAD deficiency, or for galactosemia mutations in children who screened positive for that

disorder. DNA technology has the potential to be adapted to screen for numerous conditions with onset in later childhood or even adulthood. For example, there are studies underway investigating the possibility of screening for HLA haplotypes that could predict a predisposition to diabetes mellitus I or for mutations in genes that could be associated with a high risk of developing asthma.^{39,40}

For some of these "new," rare, recently discovered disorders, there is incomplete information about sensitivity and predictive value of the screening, heterogeneity of clinical presentations, response to therapy, and natural history. However, information from states that have had expanded screening for several years is encouraging,^{30,31} and the public seems to want expansion. It is likely that more will be learned about the rare disorders if newborn screening programs and their advisory committees in Delaware and elsewhere continue to collaborate; if there are effective education programs for consumers and primary care providers; if there is good collaboration among families, primary providers, and metabolic centers; and if follow-up procedures continue to be efficient.^{1,10,29-31,41,42} Outcomes for infants identified with the well-established disorders will continue to be excellent.

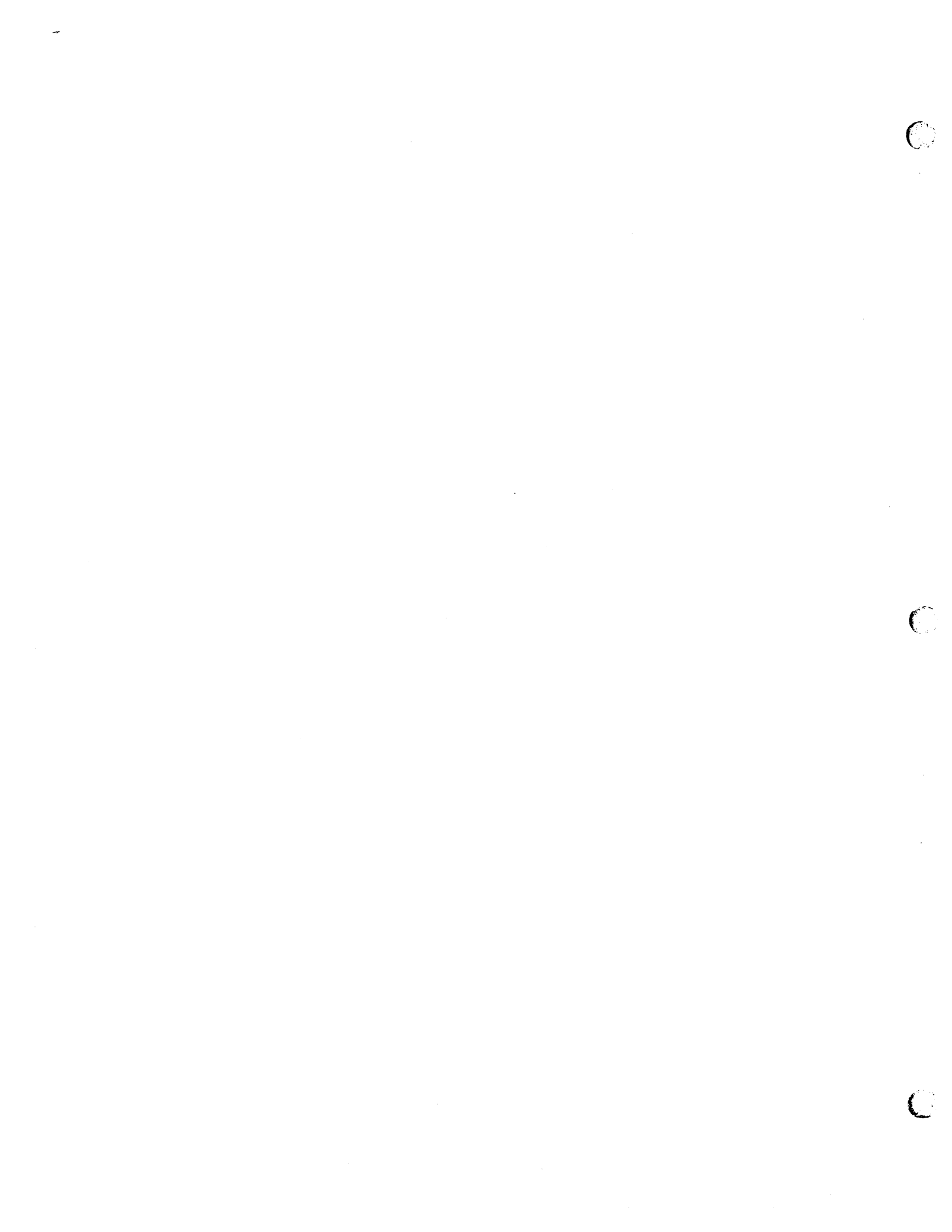
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ACKNOWLEDGEMENTS

The assistance and dedication of the Newborn Screening team in the State Laboratory in Smyrna (Dr. Jane Getchell, Director; Patricia Scott, Director of Newborn Screening laboratory procedures; BJ Scott; Clover Carlisle; Cindy Pearson; and John Pratt) and of the Newborn Screening follow-up staff (Betsy Voss; Joanne Baker, RN, MSN; Betty Pardee; Linda Braxton-Webb; Mary Carroll McCaffrey; and Kittsa Wass) are gratefully acknowledged.



APPENDIX D

**Blood Collection on Filter Paper for Newborn
Screening Program; Approved Standard
Fourth Edition, Vol. 23, No. 21**

Blood Collection on Filter Paper for Newborn Screening Programs; Approved Standard—Fourth Edition

1 Scope

1.1 Specimen Quality

The primary goal of this standard is to improve and ensure the quality of blood spots collected from newborns.¹ Unacceptable and poor quality specimens place an unnecessary burden on the screening facility, cause unnecessary trauma to the infant and anxiety to the infant's parents, potentially delay the detection and treatment of the affected infant, and could contribute to a missed or late diagnosed case. When the screening laboratory receives an unacceptable specimen, it should request another specimen according to criteria established by the testing laboratory. In all newborn screening programs, the turnaround time for analytic results is critical if treatment to prevent the adverse consequences of the condition (such as irreversible mental retardation or death) is to begin on time.

1.2 Specimen Acceptability

The only justification for refusing to analyze a specimen and declaring it unacceptable is that its analysis might yield unreliable, misleading, or clinically inaccurate values for a particular analyte. Since, by this definition, an unacceptable specimen gives no usable information, such specimens should not be analyzed, and those responsible for collecting the original specimen should be notified with all due haste so that an acceptable specimen can be obtained as soon as possible. If a specimen is analyzed, the laboratory is, in effect, acknowledging that the specimen is suitable for testing and is assuming responsibility for the reliability of the analytic values. Program-specific rules should be written and followed consistently with respect to handling specimens of insufficient quantity, especially for multianalyte test panels.

1.2.1 Other Considerations

The secondary goals of this standard are to delineate the minimum necessary information for the specimen collection form; to standardize the components of this form; to describe minimal requirements for the filter paper matrix on which the blood spots are collected; and to define the handling, shipping, and storage conditions for dried blood spot specimens.

1.3 Applications

This standard specifically addresses the collection of blood specimens for newborn screening programs¹ and applies to the collection of specimens used to detect such congenital disorders as primary hypothyroidism, phenylketonuria (PKU), galactosemia, congenital adrenal hyperplasia, biotinidase deficiency, maple syrup urine disease (MSUD), hemoglobinopathies and homocystinuria, among others. Many aspects of this standard are also appropriate and useful for the collection of dried blood spots used for DNA diagnostics, home collection devices, and a variety of new tests. In addition, most elements of this standard are applicable to blood collection on filter paper from fingerstick punctures of adolescents and adults. With older children (greater than one year of age) and adults, the palmar surface of the finger's last phalanx is most frequently used. (See the most current edition of NCCLS document H4—*Procedures and Devices for Collection of Diagnostic Blood Specimens by Skin Puncture*.)

2 Source of Blood

2.1 Heel

Blood collected from the heel is preferred for newborn screening and should be collected from the most medial or lateral portion of the plantar surface of the heel. “Medial” is defined as closest to the midline of the body; “lateral” is defined as away from the midline of the body; and “plantar surface” as the walking surface of the foot (see Appendix A).^{2,3,4} Previous puncture sites or the curvature of the heel must *not* be used.

2.2 Other

Cord blood, venous blood (dorsal hand vein or umbilical venous catheter specimens), and arterial blood (umbilical arterial catheter specimens) might be appropriate for special situations. (See Sections 3.1 through 3.4.) Consult local regulations and institutional policies for the collection of such specimens.

2.3 Unacceptable Sources

2.3.1 Sites From Which Blood Must Not Be Obtained:

- (1) Central area of an infant’s foot (arch), because this might result in injury to nerves, tendons, and cartilage and offers no advantage over puncturing the heel. (See the most current edition of NCCLS document H4— *Procedures and Devices for the Collection of Diagnostic Blood Specimens by Skin Puncture*.)
- (2) Fingers of a newborn, since the distance from the skin’s surface to the bone in the thickest portion of the last segment of each finger of newborns ranges from 1.2 to 2.2 mm, and the available lancets could easily damage the bone. In newborns, local infection and gangrene might be a complication of finger punctures.⁴ (See the most current edition of NCCLS document H4— *Procedures and Devices for the Collection of Diagnostic Blood Specimens by Skin Puncture*.)
- (3) Earlobe, because this might cause excessive bleeding.
- (4) A swollen or previously punctured site, because accumulated tissue fluid will contaminate the blood specimen.
- (5) Intravenous lines that are contaminated with substances (such as amino acid solutions) that might adversely affect the test results.

3 Techniques for Blood Collection on Filter Paper

3.1 Heelstick (Method of Choice)

3.1.1 Preliminary Steps

Ensure that the expiration date of the specimen collection device (card) has not passed. Complete the required patient information included on the collection device (card) either manually or electronically. In manual applications a ballpoint pen should be used; soft-tip pens will not copy through to the other sheets of paper. Address imprint devices (or adhesive labels) should never be used unless the handling process ensures that patient information is not obscured and the blood collection area is not compromised. Do not use a typewriter or printers that might compress the paper. Avoid touching the area within the circles on the filter paper section before, during, and after collection (blood spots) of the specimen. Do not allow

water, feeding formulas, antiseptic solutions, glove powder, hand lotion, or other materials to come into contact with the specimen card before or after use.

3.1.2 Precautions

Confirm the identity of the infant and ensure accuracy of the demographic data on the card. Wash hands vigorously before proceeding. All appropriate precautions, including wearing powder-free gloves (changing gloves between infants), should be taken for handling blood and disposing of used lancets in a biohazard container for sharp objects. Follow local recommendations regarding use of latex gloves in situations of latex allergy. (See the most current version of NCCLS document M29— *Protection of Laboratory Workers from Occupationally Acquired Infections*.)

3.1.3 Site Preparation

Warm the newborn's heel, since warming the skin-puncture site can help increase blood flow. A warm, moist towel or diaper at a temperature no higher than 42 °C may be used to cover the site for three minutes. This technique increases the blood flow sufficiently and will not burn the skin.⁵ (See the most current edition of NCCLS document H4— *Procedures and Devices for the Collection of Diagnostic Blood Specimens by Skin Puncture*.) Acceptable heel warming devices are also commercially available. In addition, positioning the infant's leg lower than the heart will increase venous pressure. (**Caution:** Before topical anesthetic creams are used for a heel puncture, the testing laboratory should document that these creams do not produce analytic interferences.)

3.1.4 Cleaning the Site

The skin should be wiped with alcohol (isopropanol/water: 70/30 by volume, "70%"). Allow the skin to air dry.

3.1.5 Puncture

To obtain sufficient blood flow, puncture the infant's heel on the plantar surface of the heel with a sterile lancet or with a heel incision device.^{1,6} The incision device provides excellent blood flow by making a standardized incision 1.0 mm deep by 2.5 mm long. (See the most recent edition of NCCLS document H4—*Procedures and Devices for the Collection of Diagnostic Blood Specimens by Skin Puncture*). Any puncture device used should be selected so that the puncture does not exceed 2.0 mm in depth (see reference 4 for more details). For infant safety, scalpel blades or needles must not be used to puncture the skin for blood collection. Disposable skin puncture lancets of different designs are commercially available for performing the heel stick on infants.⁶ For worker safety, disposable skin puncture devices that protect the user from unintentional self-inflicted skin punctures should be used.⁷

In small, premature infants, the heel bone (calcaneus) might be no more than 2.0 mm beneath the plantar heel skin surface and half this depth at the posterior curvature of the heel. Studies indicate that for some infants (including full-term infants) a puncturing depth beyond 2.0 mm might be excessive and might cause bone damage.^{6,8,9} In this situation other collection methods should be considered (see Section 2.2).

3.1.6 Direct Application

After the heel has been punctured, wipe away the first drop of blood with a sterile gauze pad or cotton ball and allow a large drop of blood to form. (Intermittently apply gentle pressure to the heel with the thumb, and ease this pressure as drops of blood form [see Section 3.1.6.1]). Touch the filter paper gently against the large blood drop and, in one step, allow a sufficient quantity of blood to soak through and completely fill a preprinted circle (Section 5.1 [14]) on the filter paper. *Do not press the filter paper against the puncture site on the heel.* Blood should be applied only to one side of the filter paper. Both sides of the filter paper should be examined to assure that the blood uniformly penetrated and saturated

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the paper. After blood has been collected from the heel of the newborn, the foot should be elevated above the body, and a sterile gauze pad or cotton swab pressed against the puncture site until the bleeding stops. It is not advisable to apply adhesive bandages over skin puncture sites on newborns.² (For treatment of the puncture site after specimen collection, see the current edition of NCCLS document H4—*Procedures and Devices for the Collection of Diagnostic Blood Specimens by Skin Puncture*.)

3.1.6.1 Milking

Excessive milking or squeezing the puncture might cause hemolysis of the specimen or result in an admixture of tissue fluids with the specimen and might adversely affect the test result.

3.1.6.2 Layering

Do not apply layers of successive blood drops to the same printed circle. Applying successive drops of blood to already partially dried spots causes nonuniform analyte concentrations and invalidates the specimens.

3.1.7 Collection

Collect the required number of uniform blood spots. Failure to collect the appropriate number of blood spots might invalidate the specimen for all tests depending on screening program rules (see Section 1.2). If blood flow diminishes so that a circle is not completely filled, repeat the sampling technique using a new circle or, if necessary, a new blood collection card (see Sections 3.1.3 through 3.1.6) Consult local regulations and institutional policies concerning minimum numbers of blood spots required.

3.2 Capillary Tube

Although not the method of choice, specimens can be obtained by applying blood collected in sterile heparinized capillary tubes to the collection device (see Section 3.3). EDTA might cause interference with some laboratory tests (see Section 3.3). The capillary tube collection method may also apply to cord or venous blood transferred onto filter paper. (See the most current edition of NCCLS document H4—*Procedures and Devices for the Collection of Diagnostic Blood Specimens by Skin Puncture*.) Consult appropriate local regulations and institutional policies for specific applications.

3.2.1 Collection

Using a fresh capillary tube for each circle to be filled on the screening card, collect the appropriate volume of blood (75 μL or 100 μL in U.S. screening programs) (see Section 5.1 [14]) into a heparinized capillary tube. (**Note:** The appropriate volume of the patient specimen is defined by the screening program to match that of the test calibrators and controls.)

Touch the tip of the heparinized capillary tube to the blood drop formed at the heel puncture site (see Section 3.1.5). Allow blood to flow into the tube by capillary action. Fill rates might be improved by holding the tube in a near-horizontal position when touching to the blood drop. Collect the required number of uniform blood spots. Failure to collect the appropriate number of blood spots might invalidate the specimen for all tests depending upon screening program rules (see Section 1.2).

3.2.2 Application

After filling a capillary tube to the calibration mark, immediately apply the contents of that tube to the center of a single, preprinted circle on the filter paper, completely filling the circle. Waiting too long before application will allow cells and plasma to separate. To avoid damaging the filter paper fibers, do not allow the capillary tube to touch the filter paper. Actions such as “coloring in” the circle, repeated

dabbing around the circle, or any technique that might scratch, compress, or indent the paper should not be used. Do not reuse capillary tubes.

Apply blood to only one side of the filter paper. Do not apply multiple capillary specimens to the same circle, since caking or heterogeneous spreading will occur and might adversely affect test results. The directions in Section 3.5 should be followed to complete the procedure.

3.3 Dorsal Hand Vein

Although not the method of choice, blood collected from needle puncture of the dorsal hand vein (See the most current edition of NCCLS document H3—*Procedures for the Collection of Diagnostic Blood Specimens by Venipuncture*) and its application directly onto the preprinted circles of the filter paper is possible.^a Blood should not be drawn from an extremity into which IV fluids (including blood) are being or have been infused unless appropriate precautions are taken (see the most recent edition of NCCLS document H4—*Procedures and Devices for the Collection of Diagnostic Blood Specimens by Skin Puncture*). Consult appropriate local regulations and institutional policies for specific applications.

The routine practice of dorsal hand vein collection is discouraged. Problematic issues include:

- (1) Test results might be affected by blood from different vessel sources.^{10,11,12,13}
- (2) Hand veins might be needed for IV fluids.
- (3) Venous sampling is more invasive than a heel stick.

3.3.1 Collection and Application

Select appropriate size winged blood collection set (butterfly). Remove or shorten catheter length so blood can flow freely onto the circle on the filter paper. Use standard pediatric venous collection procedures. Collect the required number of blood spots. Failure to collect the appropriate number of blood spots might invalidate the specimen for all tests depending on screening program rules (see Section 1.2).

Syringe collection of blood for application onto a collection device (card) is not recommended because of lack of anticoagulant and time delays that could allow for clot formation and settling of cells producing heterogeneous specimens.

3.4 Umbilical Venous Catheter (UVC) or Umbilical Arterial Catheter (UAC)

Although not the method of choice, blood collected from umbilical catheters (venous or arterial) is acceptable in certain situations (e.g., sick babies or in very low birth weight babies). Although unknown, it is reasonable to expect that there might be some difference in analytic test results between blood taken from the heel and that collected by umbilical catheters. Consider repeat collection from the heel at a later time. (Consult appropriate local regulations and institutional policies.)

3.4.1 Collection and Application

Due to the fact that UAC or UVC are used to infuse antibiotics or other medicines, in order to clean the line, it is important that blood (e.g., 2 to 2.5 cc [mL]) be drawn from the line before the blood is collected for testing purposes. After cleaning the line, collect blood in a syringe and immediately apply appropriate volumes to the printed circles on the specimen collection card. It is important that the blood transfer be as quick as possible to avoid blood clotting that might invalidate the specimen for testing (see Section 3.3.1). The required number of blood spots should be collected. Failure to collect the appropriate number of blood spots might invalidate the specimen for all tests depending upon screening program rules.

^a For extensive details of this technique and application methods, see M.E. Clagg in *Laboratory Medicine* [1989;20:248-250]. An NCCLS global consensus standard. ©NCCLS. All rights reserved.

3.5 Specimen Handling and Transport

3.5.1 Drying

Avoid touching or smearing the blood spots. Allow the blood specimen to air dry on a horizontally level (see Appendix D), nonabsorbent, open surface for at least three hours at an ambient temperature of 15 °C to 22 °C. Keep the specimen away from direct sunlight (indirect room light is not usually detrimental unless accompanied by heat). Blood spots on the filter paper should not be heated, stacked, or allowed to touch other surfaces during the drying process.

3.5.2 Stacking

Since leaching (cross-contamination) between specimens might occur, specimen-to-specimen contact is not appropriate. Before placing the specimens in a container for transport (see Section 3.5.3), the dried blood spots on the collection card should be rotated 180° from the blood spots on the cards in the stack immediately above and below. If collection cards are separated by physical barriers, specimen rotation is not necessary. When stacking of exposed dried blood spots cannot be avoided, the following procedure should be used:

- (1) A fold-over cover attachment can be added to the specimen collection device (see Section 5.2.3). This attachment, added when forms are manufactured, provides protection from contamination prior to blood collection, during specimen transportation (see Section 3.5.3), and during specimen storage after analysis (see Sections 3.5.4 and 7).
- (2) Glassine paper can be placed between specimens.

3.5.3 Timing and Transport (Mailing)

Unless otherwise directed by the screening laboratory, the collection card should be transported or mailed to the laboratory within 24 hours after specimen collection, and the appropriate tracking documentation maintained. Daily courier transport is recommended whenever possible. Delays at collection sites should be avoided, and the shipping environment relative to possible delays should be structured to maximize transport efficiency. Use of sealed plastic bags or other air-impermeable shipping containers are not recommended and require humidity control (see Guidelines for Shipment: <http://www.cdc.gov/od/ohs/biosfty/driblood.htm>). Comply with local regulations and institutional policies.

Specimens should not be placed in hermetically sealed containers (e.g., plastic or foil bags). Federal postal and local transport regulations must be followed.¹⁴ If local regulations require enclosure in water-tight plastic containers for transportation, then sufficient numbers of desiccant packages must be included to ensure minimal exposure of specimens to excessive moisture.¹⁴ Indicator cards may be used to monitor humidity. Humidity and moisture are detrimental to stability of dried blood spot specimens and analyte recovery.^{15,16} Specimens known to be biohazardous should be transported with special precautions.

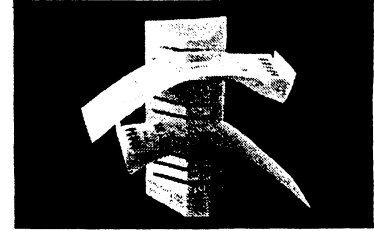
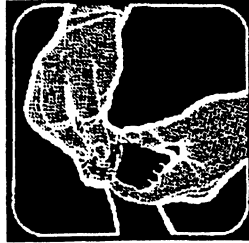
3.5.4 Storage During and After Analysis

Following receipt in the newborn screening laboratory, the specimen should be stored in a manner allowing for easy access and analysis without analytic compromise. During the analytic process, storage in a low-humidity (less than 30%)¹⁵ environment at ambient temperature is adequate. Low humidity and lower temperatures (4 °C) are suggested for program storage up to two years.¹⁵ For storage periods beyond two years see Section 7.

Appendix A. How to Collect an Acceptable Blood Spot Specimen (Detachable)

A1 Preparation

- A1.1 Wash hands vigorously.
- A1.2 Wear powder-free gloves and change gloves between infants.
- A1.3 Confirm identity of infant.



A2 Sampling Technique



- A2.1 Wearing gloves, wipe infant's heel with 70% isopropyl alcohol.
- A2.2 Allow heel to air dry.



A2.3 The puncture should be made within the shaded area as illustrated in the drawing above.

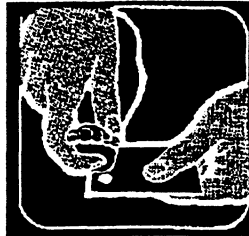


A2.4 Using a lancet of recommended length, perform puncture (depth <2.0 mm) as illustrated.

A2.5 Gently wipe off first drop of blood with sterile gauze or cotton ball. (Initial drop contains tissue fluids which might dilute sample.)

A2.6 Wait for formation of large blood droplet.

A2.7 Apply gentle pressure with thumb and ease intermittently as drops of blood form.



A2.8 Gently touch the filter paper card to the blood drop and fill each printed circle with a SINGLE application of blood. Apply blood to one side only. Observe the saturation of each printed circle as the blood flows through the filter paper.

A2.9 All used items should be disposed of in an appropriate biohazard container.

A2.10 After the specimen is collected, elevate the infant's foot and, using sterile gauze, briefly apply gentle pressure to the puncture site until the bleeding stops. Do not apply adhesive bandages.

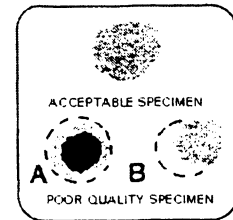
A2.11 Allow blood specimen to AIR DRY THOROUGHLY, on a horizontally level, nonabsorbent, open surface, such as a drying rack or plastic-coated test tube rack, for a minimum of 3 hours at ambient temperature. (Do not stack or heat.)

Drying rack figure reprinted with kind permission of Schleicher & Schuell BioScience, Inc.

A2.12 After the specimen has dried, place in an approved container for transport. (See local regulations.)

A3 Pitfalls

A3.1 Failure to allow residual alcohol to dry might dilute the specimen and adversely affect test results.



A3.2 Puncturing the heel on posterior curvature will permit blood to flow away from puncture, making proper spotting difficult. DO NOT USE PREVIOUS PUNCTURE SITES.

A3.3 Milking or squeezing the puncture might cause hemolysis and admixture of tissue fluids with specimen.

A3.4 Do not layer successive drops of blood on the target spot (Example A). If blood flow diminishes to incompletely fill circles, REPEAT sampling technique A2.1 through A2.10. Note Example B for poor quality specimen with inadequate blood.

A3.5 Avoid touching the area within the circle before and after blood collection. Do not allow water, feeding formulas, antiseptic solutions, powder from gloves or other materials to come into contact with the specimen card before or after use.

A3.6 Do not place the specimens in the transport container until thoroughly dry. Insufficient drying adversely affects test results. Use of sealed plastic bags requires desiccation. Ideally, transport specimens within 24 hours of collection.

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APPENDIX E

Delaware Speciality Formula Fund Policy

Division of Public Health

REGULATIONS FOR TITLE 16, CHAPTER 2 RELATING TO BIRTH DEFECTS

Delaware code 201 provides for the assistance with the cost of treatment of children with birth defects. Inherited Metabolic Disorders are one such birth defect for which a fund has been established to assist with the cost of treatment.

I. Purpose

Inherited metabolic disorders, if undetected and untreated, can result in severe mental retardation, and possibly death, in infancy. Universal screening and milk product substitution is now a standard of medical care. If a child diagnosed with an inherited metabolic disorder amenable to dietary treatment is not able to maintain a strict dietary regime throughout life the individual will likely be developmentally delayed.

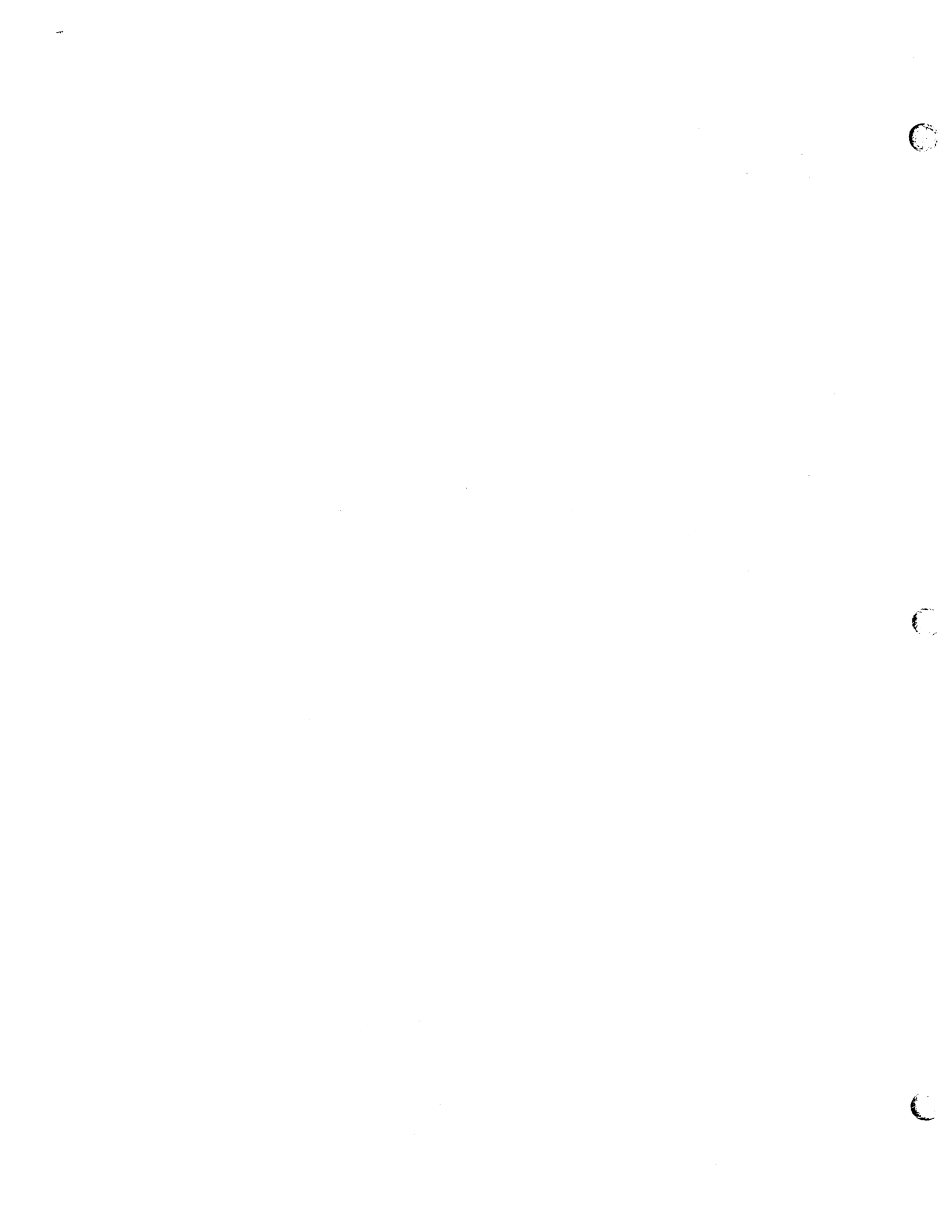
The Specialty Formula Fund ("Fund") provides that certain expenses for specialty formula, in the on-going treatment of inherited metabolic disorders, may be covered through the Department of Health and Social Services, Division of Public Health, Specialty Formula Fund.

The purpose of the Fund is to assist families in meeting the high cost of special or metabolic formulas, required to treat inherited metabolic disorders. The Division of Public Health will work to coordinate services and reduce obstacles families encounter regarding information and resource referral.

Supporting individuals with special health care needs can place economic constraints on families. The cost of special formula may be prohibitive for some families. In situations where special formula has been prescribed by a physician, and not covered by insurance, there is justification to provide economic assistance under the Fund.

II. Definitions

- 1) "INHERITED METABOLIC DISORDER," means a disorder caused by an inherited abnormality of body chemistry, which includes those disorders screened for by the state's Newborn Screening Program located within the Division of Public Health.
- 2) "SPECIALITY FORMULA" means a milk product substitution that is intended for the therapeutic dietary treatment of inherited metabolic disorders for which nutritional requirements are established by medical evaluation.
- 3) "CASE REVIEW PANEL" means a group composed of individuals with knowledge of inherited metabolic disorders, whose purpose is to review each newly diagnosed case involving the special formula fund.



- 4) "SPECIALITY FORMULA FUND" means funds provided to the Division of Public Health by the General Assembly, for prescribed specialty formula for women of child bearing age and children with inherited metabolic disorders.

III. Eligibility

- 1) Any Delaware woman of child bearing age or child diagnosed with an Inherited Metabolic Disorder, that warrants the prescription of a specialty formula may be eligible to receive assistance through the Specialty Formula Fund if uninsured or if current insurance benefit does not include this coverage. The assistance will be based on the current Department of Health and Social Services *Ability to Pay Fee Schedule* (see attached), less the average cost of formula for a normal newborn/infant or citizen using soy based milk products annually. The Fee Schedule is adjusted annually with the revised federal poverty guidelines.
- 2) The Division of Public Health may provide assistance from the Fund to a woman of child bearing age or child diagnosed with an Inherited Metabolic Disorder, if:
 - (a) The specialty formula is prescribed as medically necessary for the therapeutic treatment of an Inherited Metabolic Disorder; and
 - (b) The specialty formula is administered under the direction of a physician; and
 - (c) The client's insurer does not provide benefits to cover prescribed formula for inherited metabolic disorder or there are special circumstances as determined by the Division of Public Health, Case Review Panel.

IV. Application

The Division of Public Health will:

- (1) Staff the Case Review Panel; and
- (2) Review and refer non-compliant woman of child bearing age, parents/guardians of children with an inherited metabolic disorder to appropriate agencies for follow-up; and
- (3) Determine, on a case by case basis, any assistance to be provided to a woman of child bearing age or child from this fund.

V. Roles/Responsibilities

- 1) The Division of Public Health will appoint a Case Review Panel to make recommendations to assist the Division of Public Health in determining the assistance provided to a woman of child bearing age or child from this fund. This group will also act as a case management team for women of child bearing age, children and their families, if necessary, with public and private providers of health care and/or insurance providers. The members may have a background in metabolic disease. The



panel may include a Geneticist, Nutritionist, Newborn Screening Program staff member, a Physician who treats metabolic disorders, and one or more community member(s). The Genetics Director will chair the Case Review Panel and the Division of Public Health will provide staff.

The Case Review Panel will meet on a regular basis to review cases and make recommendations to the Division of Public Health. All current cases will be reviewed within the first six months of initiation of the Case Review Panel. The Case Review Panel will convene, as needed, to review newly diagnosed cases.

VI. Authorization for Payment

- 1) The Division of Public Health may authorize assistance prior to the review of the Case Review Panel in cases of immediate need based on physician prescription.
- 2) The Division of Public Health may provide assistance based on the physician's prescription, recommendation of the Case Review Panel, the calculation of the quantity of formula needed, economic need, and the availability of appropriated funds.
- 3) Assistance under this fund is limited to the appropriation of the General Assembly for this purpose.
- 4) The Division of Public Health will reevaluate each case every year or if health benefit coverage changes.
- 5) Women of child bearing age or the parent or guardian of a child receiving assistance from the Fund are obligated to contact the Division of Public Health, immediately, if any changes in status or eligibility occur.

VII. Referrals

1. The Division of Public Health will accept referrals from specialty hospitals, institutions, other state agencies, primary care physicians, other health care professionals, self referrals, or referrals from the family.
2. Referrals should include the following information: client's name, parent or guardian's name, address, phone number, social security number of client, diagnosis, formula prescription type and amount per month, feeding schedule, client's age, financial information, and any pertinent medical data.

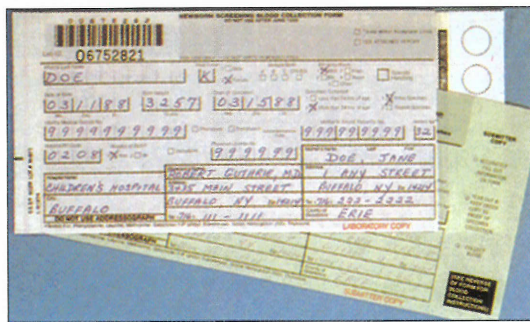


Neonatal Screening

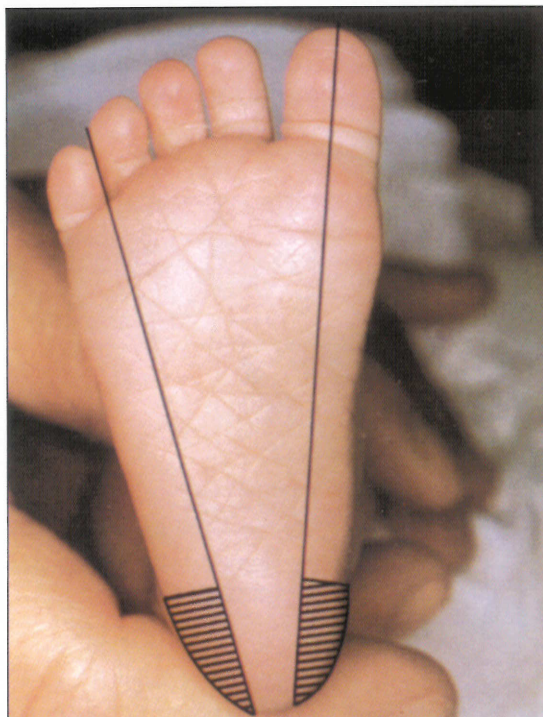
Blood Specimen Collection and Handling Procedure




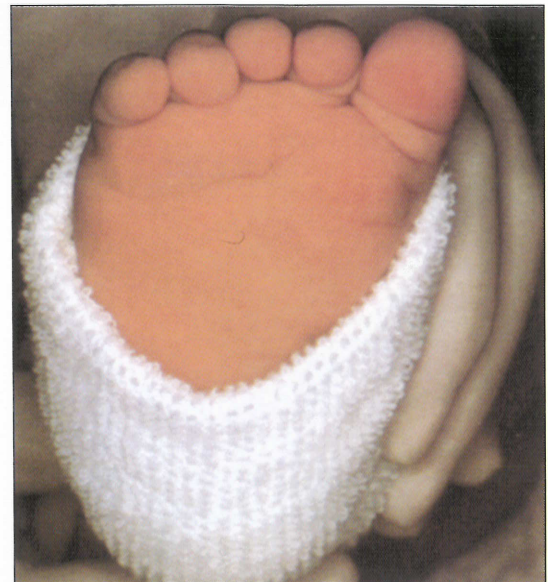
- 1 Necessary equipment: sterile lancet with tip approximately 2.0 mm, sterile alcohol prep, sterile gauze pads, soft cloth, blood collection form, gloves.



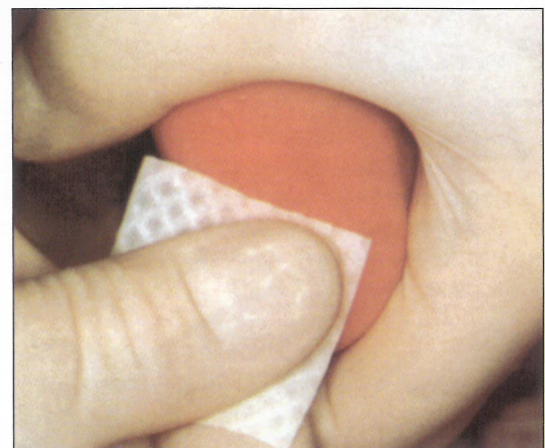
- 2 Complete ALL information. Do not contaminate filter paper circles by allowing the circles to come into contact with spillage or by touching before or after blood collection. Keep "SUBMITTER COPY" if applicable.



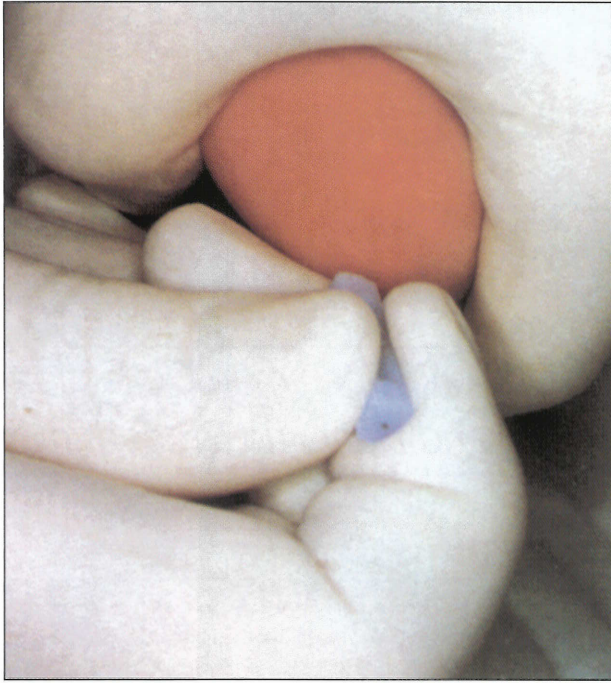
- 3 Hatched area () indicates safe areas for puncture site.



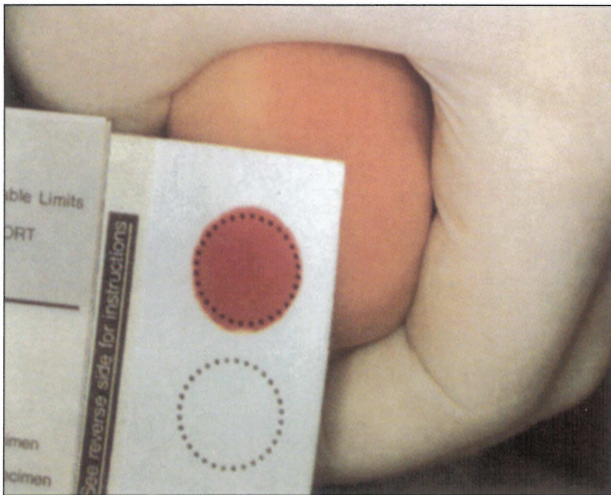
- 4 Warm site with soft cloth, moistened with warm water up to 41° C, for three to five minutes.



- 5 Cleanse site with alcohol prep. Wipe DRY with sterile gauze pad.



6 Puncture heel. Wipe away first blood drop with sterile gauze pad. Allow another LARGE blood drop to form.

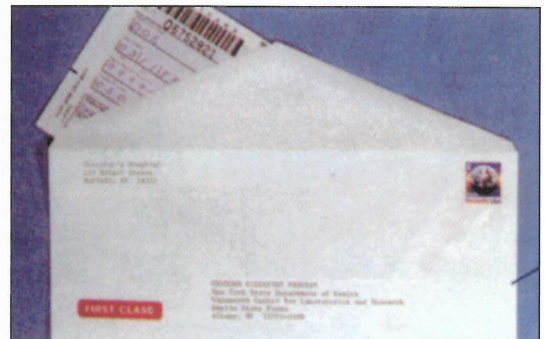


7 Lightly touch filter paper to LARGE blood drop. Allow blood to soak through and completely fill circle with SINGLE application of LARGE blood drop. (To enhance blood flow, VERY GENTLE intermittent pressure may be applied to the area surrounding the puncture site). Apply blood to one side of filter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



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

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



10 Mail completed form to testing laboratory within 24 hours of collection.

Information provided by The New York State Department of Health.

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