Introduction to the Newborn Screening Fact Sheets

Celia I. Kaye and Committee on Genetics

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American Academy of Pediatrics
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TECHNICAL REPORT

Introduction to the Newborn Screening Fact Sheets

Celia I. Kaye, MD, PhD, and the Committee on Genetics

ABSTRACT

Newborn screening fact sheets were last revised in 1996 by the Committee on Genetics of the American Academy of Pediatrics. These fact sheets have been revised again because of advances in the field, including technologic innovations such as tandem mass spectrometry, as well as greater appreciation of ethical issues such as informed consent. The fact sheets provide information to assist pediatricians and other professionals who care for children in performing their essential role within the newborn screening public health system. The newborn screening system consists of 5 parts: (1) newborn testing; (2) follow-up of abnormal screening results to facilitate timely diagnostic testing and management; (3) diagnostic testing; (4) disease management, which requires coordination with the medical home and genetic counseling; and (5) continuous evaluation and improvement of the newborn screening system. The following disorders are reviewed in the newborn screening fact sheets (which are available at www.pediatrics.org/cgi/content/full/118/3/e934): biotinidase deficiency, congenital adrenal hyperplasia, congenital hearing loss, congenital hypothyroidism, cystic fibrosis, galactosemia, homocystinuria, maple syrup urine disease, medium-chain acyl-coenzyme A dehydrogenase deficiency, phenylketonuria, sickle cell disease and other hemoglobinopathies, and tyrosinemia.

NEWBORN screening fact sheets were last revised in 1996 by the Committee on Genetics of the American Academy of Pediatrics (AAP). Publication of these revised newborn screening fact sheets was prompted by advances in the field, including technologic innovations, as well as greater appreciation of ethical issues such as those surrounding informed consent.

NEWBORN SCREENING AS A PUBLIC HEALTH SYSTEM

Every infant born in the United States is screened shortly after birth using heelstick blood spots to detect a variety of congenital conditions. Many infants are also screened for congenital hearing loss. Newborn screening programs have been developed and managed within states, the District of Columbia, Puerto Rico, the US Virgin Islands, and Guam (Table 1). As public health programs, they require a coordinated system of follow-up, diagnosis, and treatment. Periodic program evaluation is also necessary. Thus, newborn screening is not simply a test to identify whether a metabolite is found in unusually high or low concentration in a particular blood spot. Newborn screening is also more than a state-run program that ensures that each abnormal screening result is linked to a particular infant who subsequently receives a diagnostic test and, if indicated, referral for appro-

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Key Words
newborn screening, screening, genetic disorder, biotinidase deficiency, congenital adrenal hyperplasia, congenital hearing loss, congenital hypothyroidism, cystic fibrosis, galactosemia, hemoglobinopathies, homocystinuria, maple syrup urine disease, medium-chain acyl-coenzyme A dehydrogenase deficiency, phenylketonuria, sickle cell disease, tyrosinemia, tandem mass spectrometry

Abbreviations
AAP—American Academy of Pediatrics
MS/MS—tandem mass spectrometry
PKU—phenylketonuria
MCAD—medium-chain acyl-coenzyme A dehydrogenase
FAO—fatty acid oxidation

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TABLE 1 **Status of Newborn Screening in the United States**

State	Core Conditions[a]									Additional Conditions Included in Screening Panel (Universally Required Unless Otherwise Indicated)
	Hearing	Endocrine		Hemoglobin			Other			
	HEAR	CH	CAH	Hb S/S	Hb S/A	Hb S/C	BIO	GALT	CF	
Alabama	A	●	●	●	●	●	●	●		
Alaska	A	●	●	●	●	●	●	●		
Arizona	A	●	●	●	●	●	●	●		
Arkansas	●	●		●	●	●		●		
California	B	●	●	●	●	●		●		5-OXO; HHH; PRO
Colorado	●	●	●	●	●	●	●	●	●	
Connecticut	●	●	●	●	●	●	●	●	B	5-OXO; HHH; HIV[b]; NKH
District of Columbia	●	●	●	●	●	●	●	●	●	G6PD
Delaware	A	●	●	●	●	●		●		
Florida	●	●	●	●	●	●	●	●	C	
Georgia	A	●	●	●	●	●	●	●		
Hawaii	●	●	●	●	●	●	●	●		
Idaho	A	●	●	●	●	●	●	●		
Illinois	●	●	●	●	●	●	●	●		5-OXO
Indiana	●	●	●	●	●	●	●	●		
Iowa	●	●	●	●	●	●	●	●	●	HHH; NKH
Kansas	●	●		●	●	●		●		
Kentucky	A	●	C	●	●	●	C	●	C	
Louisiana	●	●		●	●	●	●	●		
Maine	A	●	●	●	●	●	●	●		HHH (A); CPS (D)
Maryland	●	●	●	●	●	●	●	●	C	
Massachusetts	●	●	●	●	●	●	●	●	A	TOXO; HHH (A); CPS (D)
Michigan	A	●	●	●	●	●	●	●		
Minnesota	A	●	●	●	●	●	●	●	●	
Mississippi	●	●	●	●	●	●	●	●	●	5-OXO; CPS; HHH
Missouri	●	●	●	●	●	●	C	●	C	
Montana	●	●	B	●	●	●	B	●	B	
Nebraska	A	●	●	●	●	●	●	●	●	5-OXO; HHH; NKH (A)
Nevada	A	●	●	●	●	●	●	●		
New Hampshire	A	●	C	C	C	C	C	●	C	TOXO
New Jersey	●	●	●	●	●	●	●	●	●	
New Mexico	●	●	●	●	●	●	●	●	C	
New York	●	●	●	●	●	●	●	●	●	HIV
North Carolina	●	●	●	●	●	●	●	●		
North Dakota	A	●	●	●	●	●	●	●	●	
Ohio	●	●	●	●	●	●	●	●		
Oklahoma	●	●	●	●	●	●		●	●	
Oregon	A	●	●	●	●	●	●	●		
Pennsylvania	●	●	●	●	●	●	B	●	B	5-OXO; CPS; G6PD; HHH; NKH (B)
Rhode Island	●	●	●	●	●	●	●	●		
South Carolina	A	●	●	●	●	●	●	●	●	
South Dakota	A	●	●	●	●	●	●	●	B	5-OXO; EMA; HHH; NKH
Tennessee	A	●	●	●	●	●	●	●		5-OXO; HHH; NKH
Texas	A	●	●	●	●	●		●		
Utah	●	●		●	●	●		●		
Vermont	A	●	●	●	●	●	●	●		CPS
Virginia	●	●	●	●	●	●	●	●	●	
Washington	A	●	●	●	●	●	●	●		
West Virginia	●	●		●	●	●		●		
Wisconsin	A	●	●	●	●	●	●	●	●	
Wyoming	●	●	●	●	●	●	●	●	●	

A dot (●) indicates that screening for the condition is universally required by law or rule; A, universally offered but not yet required; B, offered to select populations or by request; C, testing required but not yet implemented; D, likely to be detected (and reported) as a byproduct of multiple reaction monitoring screening (MS/MS) targeted by law or rule. BIO indicates biotinidase; CAH, congenital adrenal hyperplasia; CF, cystic fibrosis; CH, congenital hypothyroidism; GALT, transferase-deficient galactosemia (classical); HBS/S, sickle cell disease; HB S/C, sickle C disease; HB S/A, S-β-thalassemia; HEAR, hearing screening; 5-OXO, 5-oxoprolinuria (pyroglutamic aciduria); CPS, carbamoylphosphate synthetase; EMA, ethylmalonic encephalopathy; G6PD, glucose 6 phosphate dehydrogenase; HHH, hyperammonemia/ornithinemia/citrullinemia (ornithine transporter defect); NKH, nonketotic hyperglycinemia; PRO, prolinemia; TOXO, toxoplasmosis.

[a] Terminology is consistent with that of the American College of Medical Genetics. *Newborn Screening: Toward a Uniform Screening Panel and System*. Rockville, MD: Health Resources and Services Administration; 2005:63.

[b] Newborn screened for HIV only if mother was not screened during pregnancy.

priate treatment. Newborn screening is a 5-part system[1] in which the pediatrician plays a vital role.

Part 1: Testing of Newborn Infants

Along with the obstetrician, the pediatrician is involved in the education of parents regarding the availability of newborn screening tests, the benefits of early detection of disorders for which screening is performed, the risks that exist for newborn infants who do not receive screening, the process of screening and follow-up, and government requirements that may exist.[2] The pediatrician is also involved in obtaining informed consent in states where this is applicable. Although the timing of specimen collection is straightforward in term, healthy newborn infants, the pediatrician should be aware of factors that may influence the results of a particular screening test, including gestational and postnatal age, early discharge, diet, transfusions, and total parenteral nutrition (Table 2). Results must be documented for all patients in a timely fashion, which may be a challenge in geographic regions with large numbers of neonates, understaffed nurseries and physician offices, and poor technologic support.

Part 2: Follow-up

Proper follow-up of a "not-normal" screening result is crucial if mortality, morbidity, and disabilities are to be avoided. The primary function of the follow-up program is to locate infants with abnormal screening results and facilitate timely diagnostic testing and management. The time frame for follow-up will vary by disorder and by the degree of abnormality of the screening result. Maple syrup urine disease, congenital adrenal hyperplasia, and galactosemia are 3 disorders that can be fatal rapidly unless treatment is instituted very quickly. The pediatrician may be the provider of first contact for screen-positive infants; hence, he or she must be familiar with initial management, including referral management and subsequent diagnostic testing of such infants. The pediatrician also must be prepared to explain to the family the meaning of a positive screening result, the possibility of a false-positive test result, and the steps that must be taken next.

Part 3: Diagnostic Testing

Many of the disorders identified by newborn screening programs are heterogeneous. This variability requires specialized laboratory testing, interpretation, and treatment. The pediatrician works with specialized laboratories and providers in obtaining appropriate specimens, initiating treatment, diagnosis when appropriate, and coordinating care once the diagnosis is confirmed.

Part 4: Disease Management

Infants affected with disorders detected by newborn screening usually require lifelong management. Every

TABLE 2 Effect of Sample Timing, Preterm Birth, Diet, Transfusion, and Total Parenteral Nutrition on Newborn Screening Results

Disorder	Sample Timing	Diet	Preterm Birth	Transfusion	Total Parenteral Nutrition
Biotinidase deficiency	—	—	—	>90 d after transfusion	—
Congenital adrenal hyperplasia	↑ in false-positives first 24 h	—	↑ in false-positives secondary to normal ↑ in 17-hydroxyprogesterone	A few hours (estimated) after transfusion	—
Congenital hearing loss	—	—	—	—	—
Congenital hypothyroidism					
Thyrotropin method	↑ in false-positives before 48 h	—	—	—	—
Thyroxine method	—	—	↑ in false-positives and false-negatives	—	—
Cystic fibrosis	↑ in false-positives in first 24 h	Not known	Not known	Interferes with mutation analysis for 3–6 wk	—
Galactosemia					
Galactose method	—	Galactose-containing formula	—	—	False-negative
GALT method	—	—	—	>90 d after transfusion	—
Homocystinuria	>24 h; second test at 2–4 wk advisable	Adequate protein intake	—	—	False-positive
Maple syrup urine disease	—	—	—	—	False-positive
MCAD deficiency	Before 8 d	—	—	—	—
PKU	—	Adequate protein intake	—	—	False-positive
Sickle cell diseases and other hemoglobinopathies	—	—	↑ in false-negatives with extreme preterm birth	>90 d after transfusion	—
Tyrosinemia	—	Adequate protein intake	Increased likelihood of neonatal tyrosinemia	—	False-positive

— indicates no impact; ↑, increase.

child should have a medical home to coordinate care; that care should be accessible, family centered, continuous, comprehensive, coordinated, compassionate, and culturally competent.[3] The pediatrician plays a central role in the development of the medical home, which includes experts who understand the etiology, pathophysiology, clinical heterogeneity, and psychosocial issues associated with the disorder. Genetic counseling, including discussion of carrier testing of family members and prenatal diagnosis of future pregnancies, may be indicated.

Part 5: Evaluation

The newborn screening system can function optimally only when its components are coordinated, which means that there must be regular and timely communication between nurseries, screening laboratories, state health departments, pediatricians, and subspecialists. To ensure that this is happening, the effectiveness of each component of the system must be assessed continuously through the collection and analysis of data, including outcomes data. Although an adequate evaluation program has not been developed for most newborn screening systems, the pediatrician will be central to the implementation of such a program, particularly through the provision of outcomes data.

NEWBORN SCREENING TASK FORCE REPORT

Several factors have contributed to the need for review of the newborn screening system, including enhanced public interest in newborn screening as a universal genetic screening program; the introduction of new technologies such as tandem mass spectrometry (MS/MS) and DNA-based tests; and changing demographics, which emphasize the importance of human variation and cultural competence. In response to this need, the AAP, with support from the Health Resources and Services Administration and the National Institutes of Health, convened a task force to review the role and operation of newborn screening as a public health system.[4] The Newborn Screening Task Force outlined a national agenda to strengthen state newborn screening systems through the development of model regulations for disease and test selection; minimum standards for sample collection and other activities; model guidelines for follow-up, diagnosis, and treatment; strategies to inform families and the public more effectively; and demonstration projects to evaluate technology, quality assurance, and health outcomes. The task force report emphasized the need for a sixth component of the 5-part newborn screening system: education of professionals and the public.

INFORMED CONSENT

With the introduction of DNA-based testing as a component of newborn screening panels, consumers, health care professionals, and policy makers have become increasingly aware of issues of informed consent for both the performance of the screening tests and retention and use of residual test samples. Although all states require newborn screening, most newborn screening laws or regulations provide exemptions in some situations.[5] Expert panels have not reached consensus, but in general, they have recognized the benefit of informed consent before testing as a tool for educating parents.[6] When the validity and utility of the test have been established, experts have usually concluded that informed consent for newborn screening could be waived.[7] The Newborn Screening Task Force emphasized the need for education and concluded that, "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 protection for information contained in all newborn screening results."[4] The consent process in each state is governed by state law.

Among the benefits, newborn screening may:

- detect a serious, treatable disorder before symptoms are present;
- lead to treatment that can prevent serious problems including mental retardation and death; or
- detect carriers of certain genetic disorders.

Among the risks, newborn screening may:

- fail to identify some children who actually have the condition;require repeat testing;
- cause parental anxiety after false-positive results;
- reveal (through genetic tests) misattributed paternity; or
- detect disorders for which treatment is not effective.

There is agreement that policy guidelines for residual sample retention and use are needed, but to date, there has been no consensus on the content of such guidelines.

MS/MS

Population screening for phenylketonuria (PKU) began in the 1960s using a relatively simple analytic method. New disorders were added as methods to use blood spots were developed and were applicable to large populations at low cost. By the 1990s, scientific advances and technologic innovations led to the possibility of adding numerous new metabolic disorders to the screening panel using MS/MS (Table 3). Consumers throughout the nation acted quickly through their state legislatures to mandate the addition of medium-chain acyl-coenzyme A dehydrogenase (MCAD) deficiency and other disorders of fatty acid oxidation (FAO) to the list of disorders for which newborn screening is mandated. Several states

TABLE 3 **Additional Disorders Detected by MS/MS Screening**

	Description
Amino acid disorders	
Argininosuccinic aciduria	A disorder of the urea cycle. Episodes of hyperammonemia produce acute intoxication. The major symptoms include mental retardation, failure to thrive, liver dysfunction, unusual hair (trichorrhexis nodosa), and seizures.
Citrullinemia	A disorder of the urea cycle. Episodes of hyperammonemia produce coma and seizures. The major symptoms include changes in sensorium (irritability, lethargy), seizures, ataxia, and mental retardation.
Hypermethioninemia	Can be seen in a variety of conditions. It is found in conjunction with homocystinuria and tyrosinemia. Neonatal hypermethioninemia can occur in preterm infants or be attributable to neonatal hepatitis or a combination of factors.
FAO disorders	
Carnitine/acylcarnitine translocase deficiency	Major symptoms are fasting hypoglycemia with seizures and coma, cardiomyopathy, arrhythmias, muscle weakness, and hepatomegaly/abnormal liver function.
3-Hydroxy long-chain acyl-coenzyme A dehydrogenase (LCHAD) deficiency	Results in an inability of the body to break down fatty acids into a usable energy source. LCHAD deficiency can present as hypoglycemia, lethargy, SIDS, hypotonia, and cardiomyopathy.
MCAD deficiency	Can cause recurrent episodes of hypoglycemia, failure to thrive, persistent vomiting, hepatomegaly, and rhabdomyolysis. Acute episodes are usually associated with concurrent illness or fasting and occur in infancy or early childhood.
Multiple acyl-coenzyme A dehydrogenase deficiency (also known as glutaric acidemia-type II)	Often associated with unexplained death in neonates. Other features include respiratory distress, hypotonia, unusual odor (described as "sweaty feet") and liver dysfunction.
Neonatal carnitine palmitoyl transferase deficiency-type II	Symptoms include hypoketotic hypoglycemia with seizures and coma, cardiac arrhythmia, cardiomyopathy, and hepatopathy.
Short-chain acyl-coenzyme A dehydrogenase (SCAD) deficiency	Patients with SCAD deficiency have failure to thrive, developmental delays/hypotonia, metabolic acidosis, recurrent emesis, and a lipid-storage myopathy.
Short-chain hydroxy acyl-coenzyme A dehydrogenase deficiency	The major symptom is hypoketotic hypoglycemia.
Trifunctional protein deficiency	Can present as skeletal myopathy, cardiomyopathy, or SIDS.
Very long-chain acyl-coenzyme A dehydrogenase deficiency	Symptoms are similar to other FAO defects.
Organic acid disorders	
3-Hydroxy-3-methylglutaryl-coenzyme A lyase deficiency	This enzyme catalyzes the final step of leucine catabolism and plays a key role in ketone body formation. The major clinical features are metabolic acidosis and hypoglycemia. Unexplained fevers can occur. Encephalopathy (somnolence, coma, and malaise) and hepatopathy are common. SIDS may occur.
Glutaric acidemia type I	Results from an inherited defect in the degradation of lysine and tryptophan. Macrocephaly with an increase in the size of the extra cerebral fluid spaces occurs before the onset of any neurologic symptoms. Neurologic disease usually presents later in infancy with tonal abnormalities and choreoathetosis secondary to basal ganglia injury.
Isovaleric acidemia	This is a disorder of branched-chain amino acid metabolism that results in recurrent episodes of emesis, dehydration, and severe metabolic acidosis. Other symptoms include anorexia, listlessness, lethargy, neuromuscular irritability, and hypothermia. Acute episodes are associated with concurrent illnesses or high dietary protein intake.
Methylmalonic acidemia	An increase in methylmalonic acid can be seen with a variety of conditions. Transient increases in methylmalonic acid can be detected in otherwise healthy infants. Symptoms can include failure to thrive, episodic dehydration, and hypotonia. A variety of central nervous system changes (dystonia, dysphagia, and dysarthria) can occur. Infants with methylmalonic acidemia have been noted to have distinct facial dysmorphism.
Propionic acidemia	Symptoms are usually episodic emesis, dehydration, and metabolic acidosis. Hematologic abnormalities such as neutropenia, thrombocytopenia, and hypogammaglobulinemia are common. Mental retardation is a consistent feature, and most patients exhibit intolerance to dietary protein.
Multiple-coenzyme A carboxylase deficiency	This is a deficiency of the enzyme that attaches biotin to enzyme proteins that then results in multiple secondary enzyme deficiencies. Symptoms can be linked to deficiencies of the individual enzymes. Recurrent episodes of emesis, metabolic acidosis, and seizures can occur.
Other organic acidemias detected by MS/MS screening	2-Methylbutyryl-coenzyme A dehydrogenase deficiency, 3-methylcrotonyl-coenzyme A carboxylase deficiency, 3-methylglutaconyl-coenzyme A hydratase deficiency, mitochondrial acetoacetyl-coenzyme A thiolase deficiency (3-ketothiolase deficiency)
Other abnormal profiles	Abnormal results may be found on MS/MS screening secondary to hyperalimentation, liver disease, or contamination of the specimen. Also, treatment with medium-chain triglyceride oil, benzoate, valproate, or pyvalic acid can produce abnormal results.

SIDS indicates sudden infant death syndrome.

TABLE 4 **Status of Newborn Screening in the United States: Core Conditions Detected by MS/MS**

State	Core Conditions: Metabolic[a]																				
	Fatty Acid Disorders					Organic Acid Disorders									Amino Acid Disorders						
	CUD	LCHAD	MCAD	TFP	VLCAD	GA-I	HMG	IVA	3-MCC	Cbl-A,B	BKT	MUT	PROP	MCD	ASA	CIT	HCY	MSUD	PKU	TYR- I	
Alabama	●		●							●		●	●			●	●	●	●	●	
Alaska	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
Arizona																	●	●	●		
Arkansas																			●		
California	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
Colorado	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	●	C	
Connecticut	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
District of Columbia	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
Delaware		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
Florida	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
Georgia			●														●	●	●	●	
Hawaii	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
Idaho	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
Illinois		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
Indiana	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
Iowa	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
Kansas																			●		
Kentucky	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
Louisiana			A												A	A	A	A	●		
Maine	D	●	●	D	●	●	●	●	●	●	●	●	●	D	●	●	●	●	●	●	
Maryland		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
Massachusetts	D	A	●	D	A	A	A	A	A	A	A	A	A	D	A	A	●	●	●	A	
Michigan	A	A	●	A	A	A	A	A	A	A	A	A	A	A	●	●	●	●	●	A	
Minnesota	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
Mississippi	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
Missouri		●	●	●	●	●	●	●	●	●			●		●	●	●	●	●		
Montana	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	●	B	
Nebraska		A	●	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	●	A	
Nevada	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
New Hampshire			C														●	●	●		
New Jersey		A	●	A	●	●	●	●	●	●	A	●	●		●	●	A	●	●	A	
New Mexico	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	●	C	
New York	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
North Carolina		●	●	●	●	●	●	●	●	●	●	●	●		●	●	●	●	●		
North Dakota		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
Ohio		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●		
Oklahoma			C																●		
Oregon	A	●	●	A	●	●	●	●	●	A	A	●	●	A	●	●	●	●	●	●	
Pennsylvania	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	●	●	B	
Rhode Island	D		●														●	●	●		
South Carolina	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●		
South Dakota	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
Tennessee		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
Texas																			●		
Utah	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
Vermont	D	●	●	D	●	●	●	●	●	●	●	●	●	D	●	●	●	●	●	●	
Virginia	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
Washington			●														●	●	●		
West Virginia																			●		
Wisconsin	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
Wyoming																			●		

A dot (●) indicates that screening for the condition is universally required by law or rule; A, universally offered but not yet required; B, offered to select populations or by request; C, testing is required but not yet implemented; D, likely to be detected (and reported) as a byproduct of multiple reaction monitoring screening (MS/MS) targeted by law or rule. 3-MCC indicates 3-methylcrotonyl-coenzyme A carboxylase; ASA, argininosuccinate acidemia; BKT, β ketothiolase (mitochondrial acetoacetyl-coenzyme A thiolase; short-chain ketoacyl thiolase; T2); CBL A,B, methylmalonic acidemia (vitamin B_{12} disorders); CIT I, citrullinemia type I (Argininosuccinate synthetase); CUD, carnitine uptake defect (carnitine transport defect); GA-1, glutaric acidemia type 1; HCY, homocystinuria (cystathionine β synthase); HMG, 3-hydroxy 3-methylglutaric aciduria (3-hydroxy 3-methylglutaryl-coenzyme A lyase); IVA, isovaleric acidemia (isovaleryl-coenzyme A dehydrogenase); LCHAD, long-chain L-3- hydroxyacyl-coenzyme A dehydrogenase; MCD, multiple carboxylase (holocarboxylase synthetase); MSUD, maple syrup urine disease (branched-chain ketoacid dehydrogenase); MUT, methylmalonic acidemia (methylmalonyl-coenzyme A mutase); PROP, propionic acidemia (propionyl-coenzyme A carboxylase); TFP, trifunctional protein deficiency; TYR-1, tyrosinemia type 1; VLCAD, very long-chain acyl-coenzyme A dehydrogenase.

[a] Terminology is consistent with report from the American College of Medical Genetics. *Newborn Screening: Toward a Uniform Screening Panel and System*. Rockville, MD: Health Resources and Services Administration; 2005:63.

Nomenclature source: National Newborn Screening and Genetic Resource Center (http://genes-r-us.uthscsa.edu).

now require screening for MCAD deficiency and other disorders of FAO[8] (Table 4), and a cost/benefit analysis of MS/MS has been published.[9] MS/MS technology can also be used to screen for PKU and some other amino acid disorders and has a rate of false-positive results that is lower than other screening methods. Therefore, states that adopt MS/MS technology to screen for FAO disorders may also revise their panels of amino acid disorders for which they screen (Table 5). In addition, certain screening methods for particular disorders permit the diagnosis of other conditions that were not originally designated on the list of disorders for newborn screening. These have been called "secondary-target conditions" (Table 6). Pediatricians, who are central to the newborn screening system as discussed earlier, will need to be familiar with these new disorders as they are added to screening panels or are diagnosed because the technology for newborn screening identifies them (secondary-target conditions).

ROLE OF DNA ANALYSIS IN NEWBORN SCREENING

Analysis of DNA for mutations is not a primary screening method for any of the disorders for which newborn screening is performed today. However, secondary DNA analysis may be used in conjunction with other tests to decrease the rate of false-positive results. It may also be used as a diagnostic test for certain disorders.

CONCERNS AND CONTROVERSIES

Because the initial test in the newborn screening process is a screening test, there is a significant risk of false-positive (abnormal test, normal infant) and false-negative (normal test, affected infant) results. False-positive results lead to additional testing and parental anxiety, and long-term consequences such as the vulnerable-child syndrome may occur. False-negative results may lead to a delay in diagnosis, because the health care professional may be falsely reassured by a normal newborn screening result. These possibilities raise clinical and ethical issues, which should be discussed with parents before testing.

There is a lack of uniformity between states regarding the diseases screened and the technology used. Such lack of uniformity results in the place of birth determining the likelihood of early diagnosis of these serious but treatable conditions. Newborn screening rules and statutes require that a newborn infant be screened using the panel in the state in which he or she was born, not necessarily the state in which the mother is a resident. There is also controversy regarding whether newborn screening should incorporate conditions for which highly effective interventions that reduce morbidity for the child are unavailable. Numerous state and national organizations have convened groups to discuss these issues and propose policies, but no national consensus has been developed.[10] Finally, it must be emphasized that "normal" results of newborn screenings do not rule out the presence of these disorders, because some variants of these conditions may have onset later in life, and false-negative results may occur. The clinical judgment of the pediatrician remains the most important tool in the diagnosis of all of these conditions.

INDEX OF NEWBORN SCREENING FACT SHEETS

The following newborn screening fact sheets are available at www.pediatrics.org/cgi/content/full/118/3/e934:

- Biotinidase deficiency
- Congenital adrenal hyperplasia
- Congenital hearing loss
- Congenital hypothyroidism
- Cystic fibrosis
- Galactosemia
- Homocystinuria
- Maple syrup urine disease (branched-chain ketoaciduria)
- MCAD deficiency
- PKU
- Sickle cell disease and other hemoglobinopathies
- Tyrosinemia

TABLE 5 **Use of MS/MS for Newborn Screening**

By MS/MS Only	By MS/MS or Other Technique[a]	Not By MS/MS
Argininemia	Congenital adrenal hyperplasia	Biotinidase
Argininosuccinic acidemia	Galactosemia	Cystic fibrosis
Citrullinemia	Hemoglobinopathies	Hearing loss
Hypermethioninemia	Homocystinuria	Hypothyroidism
Hyperornithinemia-hyperammonemia-homocitrullinuria	Maple syrup urine disease	
FAO disorders (such as MCAD deficiency)	PKU	
Organic acidemias	Tyrosinemia	

This is not a comprehensive list of disorders for which newborn screening is possible.
[a] Most states use a method other than MS/MS to screen for these disorders.

TABLE 6 Status of Newborn Screening in the United States: Disorders Detected Secondary to Testing for Another Condition

State	Secondary-Target Conditions[a]																								
	Fatty Acid Disorders								Organic Acid Disorders						Amino Acid Disorders								Other Metabolic Disorders		HbG, Variant Hemoglobins
	CACT	CPT-Ia	CPT- II	DE-RED	GA-II	MCKAT	M/SCHAD	SC AD	2M3HBA	2MBG	3MGA	Cbl-C,D	IBG	MAL	ARG	BIOPT-BS	BIOPT-RG	CIT-II	H-PHE	MET	TYR- II	TYR- III	GALE	GALK	
Alabama												●						●	●		●	●			A
Alaska	●	●	●		●			●	●	●	●	●	●	●	●	B	B	●	●	●	●		B	B	●
Arizona																			●						A
Arkansas																			●				●	●	A
California	●	●	●		●			●	●	●	●	●	●	●	●	A	A	●	●	●	●	●			●
Colorado	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C			C	●	C	C	C			●
Connecticut	●	●	●	●	●			●				●		●	●				●	●			●	●	A
District of Columbia	●	●	●	●	●	A	●	●	A	●	●	●	●	●	●	A	A	●	●	●	●	A	●	●	A
Delaware	●		●		●	A		●	A	●	A	●	●		●	A	A	●	●	●	●	●	●	●	●
Florida	●	●	●		●			●				●						●	●	●	●				A
Georgia																B	B		●				●	●	●
Hawaii	●	●	●		●			●	●	●	●	●	●	●	●	B	B	●	●	●	●		B	B	A
Idaho	●	●	●		●			●	●	●	●	●	●	●	●	B	B	●	●	●	●		B	B	●
Illinois	●	●	●		●		●	●		●	●	●	●	●	●			●	●	●	●	●	●	●	A
Indiana	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●			A
Iowa	●	●	●		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●			A
Kansas																			●						A
Kentucky								●											●						A
Louisiana																			●						A
Maine	D	D	●		●			●		D	D	●	D		●			●	●	D	●	D	●	●	●
Maryland	●		●		●		●	●		●	●	●	●		●	B	B	●	●	●	●	●	●	●	A
Massachusetts	D	D	A		A			A		D	D	A	D		A			A	●	D	A	D	●	●	●
Michigan	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A			●	●						A
Minnesota	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Mississippi	●	●	●	A	●	A	●	●	A	●	●	●	●	●	●	A	A	●	●	●	●	A	●	●	●
Missouri	●	●	●		●			●				●						●	●	●	●	●			●
Montana	B		B	B	B	B	B	B		B	B	B	B	B		B	B	B	●	B	B	B			●
Nebraska	A		A		A			A		A		A	A	A	A			A	●	A	A		●	●	A
Nevada	●	●	●		●			●	●	●	●	●	●	●	●	B	B	●	●	●	●		B	B	A
New Hampshire																			●	D			●	●	B
New Jersey	A		A		A		A	●		A	A	●	A	A		●	●	●	●	A	A	A			A
New Mexico																			●						A
New York	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●			●	●	●	●	●			●
North Carolina					●			●		●		●	●						●	●	●	●			A
North Dakota	●	●	●		●	●	●	●	●	●	●	●	●	●	●			●	●		●				A
Ohio	●	●	●		●			●		●		●	●		●			●	●	●					A
Oklahoma																			●						A
Oregon	●	A	●		●			●	A	A	●	●	A	A	A	B	B	●	●	●	●		B	B	●
Pennsylvania	B	B	B	B	B		B	B		B	B	B	B	B	B	B	B	B	●	B	B	B	●	●	A
Rhode Island		D																	●				●	●	●
South Carolina	●		●		●	●		●	●	●	●	●	●			●	●	●	●	●			●	●	A
South Dakota	●	●	●		●			●		●	●	●	●	●	●			●	●	●	●	●			●
Tennessee	●	●	●	●	●			●	●	●	●	●	●	●	●			●	●	●	●	●			●
Texas																			●						A
Utah	●	●	●		●			●	●	●		●	●		●	●	●	●	●	●	●	●			●
Vermont	D	D	D		D					D	D	●			D			●	●	D	D	D	●	●	●
Virginia																			●						A
Washington																			●						A
West Virginia																			●				●	●	A
Wisconsin	●		●	●	●	●	●	●		●	●	●	●	●		●	●	●	●	●	●	●			●
Wyoming																			●						●

A dot (●) indicates that screening for the condition is universally required by law or rule; A, universally offered but not yet required; B, offered to select populations or by request; C, testing is required but not yet implemented; D, likely to be detected (and reported) as a byproduct of multiple reaction monitoring screening (MS/MS) targeted by law or rule. 2M3HBA indicates 2-methyl-3-hydroxy butyric aciduria; 2MBG, 2-methylbutyryl-coenzyme A dehydrogenase; 3MGA, 3-methylglutaconic aciduria; ARG, argininemia (arginase deficiency); BIOPT-BS, defects of biopterin cofactor biosynthesis; BIOPT-REG, defects of biopterin cofactor regeneration; CACT, carnitine acylcarnitine translocase; CBL-C,D, methylmalonic acidemia (Cbl C,D); CIT-II, citrullinemia type II; CPT-Ia, carnitine palmitoyltransferase I; CPT-II, carnitine palmitoyltransferase II; De-Red, dienoyl-coenzyme A reductase; GA-II, glutaric academia type II; GALE, galactose epimerase; GALK, galactokinase; H-PHE, benign hyperphenylalaninemia; IBG, isobutyryl-coenzyme A dehydrogenase; M/SCHAD, medium/short-chain L-3-hydroxy acyl-coenzyme A dehydrogenase; MAL, malonic academia (malonyl-coenzyme A decarboxylase); MCKAT, medium-chain ketoacyl-coenzyme A thiolase; MET, hypermethioninemia; SCAD, short-chain acyl-coenzyme A dehydrogenase; TYR-II, tyrosinemia type II; TYR-III, tyrosinemia type III.

[a] Terminology is consistent with the American College of Medical Genetics. *Newborn Screening: Toward a Uniform Screening Panel and System*. Rockville, MD: Health Resources and Services Administration; 2005:63.

Nomenclature source: National Newborn Screening and Genetic Resource Center (http://genes-r-us.uthscsa.edu).

REFERENCES

1. Pass KA, Lane PA, Fernhoff PM, et al. US newborn screening system guidelines II: follow-up of children, diagnosis, management, and evaluation. Statement of the Council of Regional Networks for Genetic Services (CORN). *J Pediatr.* 2000;137: S1–S46
2. Larsson A, Therrell BL. Newborn screening: the role of the obstetrician. *Clin Obstet Gynecol.* 2002;45:697–710; discussion 730–732
3. American Academy of Pediatrics, Medical Home Initiatives for Children With Special Needs Project Advisory Committee. The medical home. *Pediatrics.* 2002;110:184–186
4. 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. *Pediatrics.* 2000;106:2(2 pt 2): 383–427
5. United States General Accounting Office. *Newborn Screening: Characteristics of State Programs.* Report to Congressional Requesters. Washington, DC: General Accounting Office; 2003. Publication No. GAO-03-449
6. Institute of Medicine, Committee on Assessing Genetic Risks. *Assessing Genetic Risks: Implications for Health and Social Policy.* Andrews LB, Fullarton JE, Holtzman NA, Motulsky AG, eds. Washington, DC: National Academy of Sciences; 1994
7. National Human Genome Research Institute. *Promoting Safe and Effective Genetic Testing in the United States: Final Report of the Task Force on Genetic Testing.* Holtzman NA, Watson MS, eds. Bethesda, MD: National Institutes of Health; 1997
8. Centers for Disease Control and Prevention. Using tandem mass spectrometry for metabolic disease screening among newborns: a report of a work group. *MMWR Recomm Rep.* 2001;50(RR-3):1–34
9. Schoen EJ, Baker JC, Colby CJ, To TT. Cost-benefit analysis of universal tandem mass spectrometry for newborn screening. *Pediatrics.* 2002;110:781–786
10. Nelson RM, Botkjin JR, Kodish ED, et al. Ethical issues with genetic testing in pediatrics. *Pediatrics.* 2001;107:1451–1455