Expanded Newborn Screening: Information and Resources for the Family Physician

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Family physicians treat an increasing number of children with metabolic disorders identified through newborn screening, and they are often the first line of defense in responding to an abnormal screening result. How the family physician chooses to interpret information from the screening and what he or she chooses to tell the family affects the parent-child relationship, as well as the infant's medical and developmental outcomes. Family physicians must, therefore, be familiar with the current state of expanded newborn screening to effectively communicate results and formulate interventions. They also must recognize signs of metabolic disorders that may not be detected by newborn screening or that may not be a part of newborn screening in their state. For every infant identified with a metabolic disorder, 12 to 60 additional infants will receive a false-positive screening result. One recommendation for communicating results to parents is to explain what the initial and follow-up findings mean, even if the diagnosis is not confirmed. For infants with true-positive results, long-term follow-up involves regular medical examinations, communication with a metabolic treatment center, and developmental and neuropsychological testing to detect possible associated disorders in time for early intervention. This article provides a description of metabolic disorders included in expanded newborn screening programs; a list of disorders screened for in each state; and resources for obtaining ACTion sheets (guidelines for responding to newborn screening results), fact sheets, and emergency and acute illness protocols. (*Am Fam Physician*. 2008;77(7):987-994. Copyright © 2008 American Academy of Family Physicians.)

Family physicians treat an increasing number of children with metabolic and other disorders identified through newborn screening. This increase is the result of the recent recommendations by the American College of Medical Genetics, in conjunction with the Maternal and Child Health Bureau, to include 29 core conditions and 25 secondary targets (which are identified through screening for core conditions) in a uniform screening panel.[1] Although each metabolic disorder included in expanded newborn screening programs is rare, metabolic disorders in general have the potential to affect one in 2,400 infants annually.[2] Screening for nonmetabolic disorders adds to this number, culminating in a collective incidence rate of one in 1,500 infants.[3] In the absence of early detection and treatment, these disorders lead to a variety of adverse outcomes, including moderate to severe neuropsychological dysfunction, mental retardation, and death. Expanded newborn screening allows for early detection and treatment and can potentially prevent serious consequences.[4]

Routine newborn screening in the United States began in the 1960s as screening for a single biochemical genetic disorder, phenylketonuria (PKU).[5] Over the years, congenital hypothyroidism and other metabolic disorders were added to the routine screenings. In the past, testing for each disorder required a separate test and a separate disk punched from a dried blood sample on filter paper. However, recent application of tandem mass spectrometry (MS/MS) provides the opportunity to screen for many disorders with one evaluation that requires only a single blood sample.[6] Forty-seven states have adopted MS/MS technology for such screening, with the number of disorders screened for ranging from three to more than 40 *(Table 1)*.[7] The National Newborn Screening and Genetics Resource Center maintains a current list of disorders included in newborn screening by state, which is available on its Web site (http://genes-r-us.uthscsa.edu).[7]

The newborn blood sample is obtained before discharge from the hospital and sent to the screening laboratory, which generally reports results within seven days to the family physician listed on the newborn screening form.[8] Nine states require and five states recommend that the family physician obtain a second sample from all

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendations	*Evidence rating*	*References*
ACTion sheets developed by the American College of Medical Genetics should be used to determine appropriate steps after a positive newborn screening result.	C	7
Emergency care for infants with metabolic disorders must be directed by a metabolic specialist in collaboration with emergency personnel and the family physician.	C	9, 16
Personal contact with the family physician to discuss a false-positive newborn screening result reduces parental stress and misunderstanding about the screening process.	C	21, 24

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 896 or http://www.aafp.org/afpsort.xml.

Table 1. Newborn Screening for Metabolic Disorders in the United States

	Disorders										
	Amino acid and urea cycle						*Fatty acid oxidation*				
State	*ASA*	*CIT*	*HCY*	*MSUD*	*PKU*	*TYR-I*	*CUD*	*LCHAD*	*MCAD*	*TFP*	*VLCAD*
All states (except those listed below)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Alabama	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓
Arkansas*					✓						
Kansas*					✓						
Nebraska	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓
New Hampshire			✓	✓	✓				✓		
North Carolina	✓	✓	✓	✓	✓			✓	✓	✓	✓
Ohio	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓
Oklahoma*					✓				✓		
Pennsylvania†				✓	✓						
Tennessee	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓
Washington			✓	✓	✓				✓		
West Virginia*					✓						

NOTE: *Screening for conditions that are required by law or rule, and fully implemented or conditions that are likely to be detected (and reported) as a byproduct of screening for required conditions.*

ASA = argininosuccinic acidemia; CIT = citrullinemia; HCY = homocystinuria; MSUD = maple syrup urine disease; PKU = phenylketonuria/hyperphenylalaninemia; TYR-I = tyrosinemia type I; CUD = carnitine uptake defect (carnitine transport defect); LCHAD = long-chain acyl-CoA dehydrogenase deficiency; MCAD = medium-chain acyl-CoA dehydrogenase deficiency; TFP = trifunctional protein deficiency; VLCAD = very long-chain acyl-CoA dehydrogenase deficiency; 3-MCC = 3-methylcrotonyl-CoA carboxylase deficiency; BKT = beta-ketothiolase deficiency; CBL A,B = cobalamin A, B defects (methylmalonic acidemia); GA-I = glutaric acidemia type I; HMG = 3-hydroxy-3-methylglutaryl-CoA lyase deficiency; IVA = isovaleric acidemia; MCD = multiple carboxylase deficiency; MUT = methylmalonic acidemia (mutase deficiency form); PROP = propionic acidemia.

**—Screening for all other disorders required by law, but not yet implemented.*
†—Screening for all other disorders available to certain populations or by request.

Information from reference 7.

infants within one to six weeks after birth[7]; however, every state requires that the family physician respond immediately to a positive result on the first screen. Improper handling of a newborn screen can be catastrophic for the infant.

Family physicians are often the first line of defense in responding to an abnormal newborn screening result.[3] How they choose to interpret the information and what they choose to tell families affects the parent-child relationship, as well as the medical and developmental outcomes of the infant.[4] Family physicians must, therefore, be familiar with the current state of expanded newborn screening to effectively communicate results and formulate interventions. Furthermore, they must recognize signs of metabolic disorders that may not be detected by newborn screening or that may not be included in newborn screening in their state.

Organic acid								
3MCC	*BKT*	*CBL A,B*	*GA-I*	*HMG*	*IVA*	*MCD*	*MUT*	*PROP*
✓	✓	✓	✓	✓	✓	✓	✓	✓
		✓	✓		✓		✓	✓
✓	✓	✓	✓	✓	✓	✓	✓	✓
✓	✓	✓	✓	✓	✓	✓	✓	✓
✓	✓	✓	✓	✓	✓	✓	✓	✓
✓	✓	✓	✓	✓	✓	✓	✓	✓

Metabolic Disorders

Metabolic disorders detected by MS/MS can be categorized into three groups: (1) amino acid and urea cycle disorders; (2) fatty acid oxidation disorders; (3) and organic acid disorders. Severity of metabolic disorders can range from mild or benign to severe.[9] If results are not normal on the first screen, the next most common result is a "borderline" result, which indicates a value above the upper limit of normal, but below the lower limit of abnormal required for diagnosis of a particular disease. In many instances, a repeat sample will show the analyte of interest to be within the normal range, and the parents can be assured that the screening result is normal.[9]

Cut-offs for screening are determined to avoid missing potentially devastating inborn errors of metabolism that have not yet been identified, possibly because the infant has not yet been exposed to enough of the toxic nutrient. Therefore, positive screening results require immediate attention. On occasion, a markedly out-of-range result necessitates urgent action (e.g., admittance to an emergency department, examination by a metabolic specialist or clinical geneticist). If there is any uncertainty regarding results, the family physician should contact a metabolic specialist. In most states, the newborn screening program maintains a list of contact information for the biochemical or clinical geneticist on call. *Tables 2, 3,* and *4* present an overview of the most common metabolic disorders that are recommended for expanded newborn screening or that are likely to be identified as a byproduct of screening for the recommended disorders.[10-12]

Amino acid disorders include homocystinuria, maple syrup urine disease, PKU, and tyrosinemia type I *(Table 2)*.[10-12] Newborn screening has been performed for these disorders for decades. Treatment consists of protein-restricted diets supplemented with a special formula that provides the necessary parts of protein, but without the "offending" amino acid (the part of protein that the patient is unable to metabolize). Despite treatment, many children with amino acid disorders will exhibit some effects associated with the disorder, but to a lesser degree than would have occurred if the child had not been treated. These include learning disabilities, attention-deficit/hyperactivity disorder, and emotional problems.

Urea cycle disorders (e.g., citrullinemia, argininosuccinic acidemia) were recently added to newborn screening panels. Less is known about the effectiveness of early treatment; however, because these disorders can result in severe cognitive deficits, illness, and death, urgent action with treatment by a multidisciplinary team at a metabolic center is the first step. Infants with metabolic disorders associated with acute neonatal illness may exhibit neurobehavioral symptoms, such as lethargy, poor feeding, and vomiting. Parents will often note that their child "doesn't look right." Such observations require special action within the context of an abnormal newborn screening result.[9]

Fatty acid oxidation disorders are associated with central nervous system (CNS) and other clinical abnormalities, as well as mental retardation *(Table 3)*.[10-12] Treatment generally consists of avoidance of fasting and carnitine supplementation. If metabolic episodes do not occur, most infants will develop normal cognitive abilities. Medium-chain acyl-CoA dehydrogenase deficiency is the most common fatty acid oxidation disorder and may be associated with intermittent severe metabolic crises or sudden death.[13]

Organic acid disorders (e.g., glutaric acidemia type I, propionic acidemia) represent extremely volatile conditions in which episodes of acidosis occur in the newborn period or later *(Table 4)*.[10-12] CNS abnormalities and developmental delay or mental retardation may occur despite treatment with special diets, supplements, or medications. It is unknown whether early treatment attenuates these effects.[14]

Resources

The American College of Medical Genetics recently developed ACTion (ACT) sheets and algorithms for physicians and metabolic specialists to use if one of their patients receives an abnormal newborn screening result. The purpose of the ACT sheets is to outline immediate actions (e.g., stopping all feeding

Table 2. Amino Acid and Urea Cycle Disorders

Disorder	*Organ or system affected*	*Signs of metabolic instability*	*Neurodevelopmental effects (if not treated)*
Amino acid			
Homocystinuria	Eye, skeletal	Blood clots; long, thin, Marfan syndrome-like stature; dislocated lenses	Mental retardation, psychiatric problems
Maple syrup urine disease	CNS	Coma, ketoacidosis, lethargy, failure to thrive, poor feeding	Mental retardation
Phenylketonuria	CNS	Hyperactivity, seizures	Mental retardation, autism; risk of executive functioning deficits, slow reaction time, and depression; maternal phenylketonuria
Tyrosinemia type I	Liver	Liver disease	Motor deficits
Urea cycle			
Arginase deficiency	CNS	Hyperammonemia	Developmental delay, motor deficits
Argininosuccinic acidemia	CNS, liver	Hyperammonemia	Developmental delay, motor deficits, mental retardation, behavioral problems
Citrullinemia	CNS	Hyperammonemia	Developmental delay, motor deficits, mental retardation, behavioral problems
Hyperornithinemia-hyperammonemia-homocitrullinuria syndrome (ornithine transport defect; secondary urea cycle defect)	CNS	Hyperammonemia	Learning disabilities, speech delay, poor visual-motor skills, irritability, aggression, attention-deficit/hyperactivity disorder

CNS = central nervous system.

Information from references 10 through 12.

Table 3. Fatty Acid Oxidation Disorders

Disorder	*Organ or system affected*	*Signs of metabolic instability*	*Neurodevelopmental effects (if not treated)*
Carnitine transport defect	CNS, cardiovascular	Low carnitine levels	Developmental delay, motor deficits, muscle weakness
Citrullinemia type I (carnitine palmityl transferase type I deficiency)	CNS	Hypoglycemia	Developmental delay, motor deficits
Citrullinemia type II (carnitine palmityl transferase type II deficiency)	CNS, cardiovascular	Hypoglycemia	Neonatal presentation: severe mental retardation or death Later onset: muscle weakness
Glutaric acidemia type II	CNS	Hypoglycemia	Severe motor deficits or mental retardation
Short-chain acyl-CoA dehydrogenase deficiency	CNS	Hypoglycemia, acidosis	Developmental delay, motor deficits, potential for mental retardation
Medium-chain acyl-CoA dehydrogenase deficiency	CNS	Hypoglycemia, acidosis	Developmental delay, motor deficits, potential for mental retardation
Long-chain acyl-CoA dehydrogenase deficiency	CNS, eye, cardiovascular	Hypoglycemia	Developmental delay, motor deficits, potential for mental retardation, poor vision
Very long-chain acyl-CoA dehydrogenase deficiency	CNS, cardiovascular	Hypoglycemia	Developmental delay, motor deficits, potential for mental retardation

CNS = central nervous system.

Information from references 10 through 12.

Table 4. Organic Acid Disorders

Disorder	*Organ or system affected*	*Signs of metabolic instability*	*Neurodevelopmental effects (if not treated)*
3-hydroxy-3-methyglutaryl-CoA lyase deficiency	CNS	Hypoglycemia	Developmental delay, hypotonia
3-methylcrotonyl-CoA carboxylase deficiency	CNS	Hypoglycemia	Developmental delay, hypotonia; many asymptomatic
Beta-ketothiolase deficiency	CNS	Hypoglycemia	Motor deficits, mental retardation
Glutaric acidemia type I	CNS	Acidosis	Motor deficits, severe dystonia; cognition often intact
Isovaleric acidemia	CNS	Acidosis, hyperammonemia, sweaty feet odor	Developmental delay, motor deficits, mental retardation
Methylmalonic acidemia	CNS	Acidosis, hyperammonemia	Developmental delay, mental retardation, movement disorders
Propionic acidemia	CNS	Acidosis, hyperammonemia	Developmental delay, mental retardation, speech defects

CNS = central nervous system.

Information from references 10 through 12.

of the nutrient that cannot be metabolized). Management of metabolic disorders requires attention to subtle changes in the infant's metabolic status and close adherence to the treatment details. The ACT sheets provide a brief description of the disorder, an overview of the clinical consequences, and decision trees for actions. They can be accessed through a link on the National Newborn Screening and Genetics Resource Center Web site.[7]

More detailed fact sheets have been prepared on many disorders. They have been published in *Pediatrics* and are available for free on the journal's Web site (http://www.pediatrics.org/cgi/content/full/118/3/e934).[15] The fact sheets include a description of the disease as well as sections on incidence; clinical manifestations; symptomatic presentation and morbidity; mortality; pathophysiology; inheritance and genotype; rationale and benefits of newborn screening; screening methods; follow-up and diagnostic testing; disease management; and current controversies.

Acute illness protocols are also available and can be found on the New England Consortium of Metabolic Programs Web site (http://www.childrenshospital.org/newenglandconsortium/NBS/Emergency_Protocols.html).[16] Because of the complexity of treatments and the speed with which a metabolic crisis can cause death or irreversible damage, emergency care must be directed by a metabolic specialist in collaboration with emergency personnel and the family physician.[9]

False-Positive Results

For every infant identified with a true-positive screening result, 12 to 60 additional infants will receive a false-positive screening result, depending on the disorder and the specificity of the screening algorithm for that disorder.[17,18] A false-positive result occurs when the initial abnormal screening result is not confirmed with further testing. In the 1960s, the term "PKU anxiety syndrome" was used to describe the impact of a false-positive newborn screening result on parents.[19] The syndrome was characterized by acute or chronic anxiety caused by uncertainty about abnormal screening results, which led to persisting worry about the infant's health. The concept of "vulnerable child syndrome" is used to describe children whose parents experience sustained anxiety over them.[20] In a recent study of expanded newborn screening for metabolic disorders, parents of infants who received a false-positive screening result were more stressed and were more likely to worry about their infant's future compared with parents of infants who received a normal screening result.[21] Attention should be given to this group of parents.

Communicating Results

Surveys suggest that family physicians feel unprepared to communicate results from expanded newborn screening to parents[22] and to manage the follow-up of an infant

with a positive screening result.[23] In a follow-up study of families conducted approximately six months after they received a false-positive newborn screening result, parents were asked what would have made the screening experience less stressful. Results indicated that 61 percent would have liked more information.[21] Approximately 32 percent of parents reported a lag time of more than two weeks between testing and receipt of results, 50 percent reported they were never given results, and 22 percent reported that they had been advised not to worry because "no news is good news."[21] A review of the literature on communicating newborn screening results emphasized the importance of informing parents in person about the results and the need for retesting, and for explaining what the initial and follow-up findings mean, even if the diagnosis is not confirmed.[24] Brochures with information on newborn screening are available and may aid in communication with parents *(Table 5)*.

Follow-up

Long-term follow-up by the family physician includes a standard neurologic and medical examination with specific attention to hepatomegaly and cardiac and neurologic functioning.[9] A thorough medical history is obtained, including information on hospitalizations, emergency department visits, medications, treatment, and developmental milestones. Results from tests, such as echocardiography, electrocardiography, liver function tests, electrolyte measurements, clotting studies, complete blood count, and ophthalmologic examinations, provide additional data on associated effects of a disorder.

If the infant is ill or showing symptoms of metabolic crisis (e.g., lethargy, vomiting, ataxia), contact with a metabolic specialist is critical. Basic steps should be taken to stabilize the infant, including avoidance of the nutrient that cannot be metabolized, admittance to the emergency department, and initiation of anticatabolic therapy (often at higher concentrations than prescribed for infants without metabolic disorders).[16]

Developmental and neuropsychological evaluations are also important in the routine follow-up of children with metabolic disorders. If possible, psychologists familiar with metabolic disorders should perform the evaluation because they may be able to more easily recognize the subtle warning signs and symptoms associated with the disorder. The child may need treatment modifications, early intervention, or remedial help (if the child is school-age).

The family physician often walks a fine line between reassuring the family and stressing the importance of adhering to treatment recommendations. These tasks are made more difficult because of the uncertainty

Table 5. Information for Parents About Newborn Screening

Resource	*Source*	*Web site*
A Parent's Guide to Newborn Screening	Save Babies Through Screening Foundation	http://www.savebabies.org/library/HandoutAParentsGuidetoNBS.pdf
Expanded Newborn Screening: Commonly Asked Questions	Children's Hospital Boston	http://www.childrenshospital.org/newenglandconsortium/scientists_physicians2.html# (Under "Expanded newborn screening," click on "Commonly asked questions")
Follow-up to Newborn Screening: A Guide for Parents	Children's Hospital Boston	http://www.childrenshospital.org/newenglandconsortium/nbs_brochure.pdf
These Tests Could Save Your Baby's Life	U.S. Department of Health and Human Services, Maternal and Child Health Bureau	http://mchb.hrsa.gov/programs/genetics/committee/nbsbrochure.htm

associated with newborn screening results.[9] Metabolic or specialty centers may lower the risk of sending mixed messages to parents by providing detailed follow-up information to the family physician. In metabolic and other disorders identified through newborn screening, the key to optimal care often lies with the family physician who is aware of the infant's special health care needs but who maintains focus on the "whole" child within the context of his or her family and community.

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