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## Newborn Screening

### Committee on Genetics

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**ABSTRACT:** Newborn screening tests are designed to detect infants with specific conditions whose families also would benefit from early diagnosis and treatment. These conditions include disorders of metabolism, endocrinopathies, hemoglobinopathies, hearing loss, and cystic fibrosis. Each state program must have a system in place for notification, timely follow-up, and evaluation of any infant with a positive screening result. Newborn screening programs have enormous public health benefits and have been effective in identifying newborns that can benefit from early treatment.

Obstetricians need to be aware of the status of newborn screening in their states and should be prepared to address questions or refer their patients to appropriate sources for additional information. Newborn screening tests are designed to detect infants with specific conditions whose families also would benefit from early diagnosis and treatment. These conditions include disorders of metabolism, endocrinopathies, hemoglobinopathies, hearing loss, and cystic fibrosis. These screening tests secondarily may identify couples who are carriers of inherited conditions. Currently, state public health agencies fund and implement newborn screening programs for their own residents, leading to variations in practice nationwide.

Technologic advances in combination with new genetic information have led to a re-examination of the implementation and standardization of newborn screening practices across the United States. These efforts are led by the Health and Human Resources Services Administration Maternal Child and Health Bureau. As providers of obstetric services, obstetrician–gynecologists are advocates for women and play an expanded role in newborn screening (1–4). A recent report by the American Academy of Pediatrics “highlights the need for a more uniform national policy for the selection of newborn screening tests.” In response, the American College of Medical Genetics was commissioned by the Health and Human Resources Services Administration Maternal Child and Health Bureau to determine a uniform panel of core conditions appropriate for newborn

screening. Each of the 29 conditions in the core panel (Table 1) has a screening test that can be performed within 24–48 hours after birth, can be treated, and has a known natural history. It is intended that this core panel remain flexible and criteria yet to be established will be used to expand this panel in the future. Secondary targets (supplemental conditions) are conditions that can be detected using the same technology as in the detection of core conditions (Table 1). Although secondary targets are clinically important, they may lack known treatments or their natural histories may not be well understood.

Most states require newborn screening for the core panel, and a number of states require newborn screening for some conditions on the secondary panel. However, the list of conditions screened for in each state can be expected to change over time; a listing of the most current panel of conditions screened for by states can be viewed at the web site of the National Newborn Screening and Genetics Resource Center (<http://genesr-us.uthscsa.edu>).

Collection of newborn heel stick-derived blood onto filter paper specimens remains the method of sample collection. Technologic advances have enabled newborn screening to rely less on single platform tests and more on multiplex technology, such as tandem mass spectrometry (MS/MS), immunoassay, and spectrophotometry. Newborn screening may now include 1) screening for genetic conditions that relies on polymerase chain reaction and immunoassay (eg, cystic fibrosis), 2) screening for hemo-



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**Table 1.** Newborn Screening Panel: Core Panel and Secondary Targets

Tandem Mass Spectrometry				
Acylcarnitines		Amino Acids		
Conditions of Organic Acid Metabolism	Conditions of Fatty Acid Metabolism	Conditions of Amino Acid Metabolism	Hemoglobinopathies	Others
<b>CORE PANEL</b>				
Isovaleric acidemia	Medium-chain acyl-CoA dehydrogenase deficiency	Phenylketonuria	Hb SS disease (sickle cell anemia)	Congenital hypothyroidism
Glutaric acidemia type 1	Very long-chain acyl-CoA dehydrogenase deficiency	Maple syrup (urine) disease	Hb S/ $\beta$ -thalassemia	Biotinidase deficiency
3-hydroxy 3-methyl glutaric aciduria	Long-chain 3-OH acyl-CoA dehydrogenase deficiency	Homocystinuria	Hb S/C disease	Congenital adrenal hyperplasia
Multiple carboxylase deficiency	Trifunctional protein deficiency	Citrullinemia		Classic galactosemia
Methylmalonic acidemia (mutase)	Carnitine uptake defect	Argininosuccinic acidemia		Hearing loss
3-Methylcrotonyl-CoA carboxylase deficiency		Tyrosinemia type I		Cystic fibrosis
Methylmalonic acidemia (Cbl A, B)				
Propionic acidemia				
$\beta$ -Ketothiolase deficiency				
<b>SECONDARY TARGETS</b>				
Methylmalonic acidemia (Cbl C, D)	Short-chain acyl-CoA dehydrogenase deficiency	Benign hyperphenylalaninemia	Other variant hemoglobinopathies (including Hb E)	Galactokinase deficiency
Malonic aciduria	Glutaric acidemia type II	Tyrosinemia type II		Galactose epimerase deficiency
Isobutyryl-CoA dehydrogenase deficiency	Medium/short-chain 3-OH acyl-CoA DH deficiency	Defects of biopterin cofactor biosynthesis		
2-Methyl 3-hydroxy butyric aciduria	Medium chain ketoacyl-CoA thiolase deficiency	Argininemia		
2-Methylbutyryl-CoA carboxylase deficiency	Carnitine palmitoyltransferase II deficiency	Tyrosinemia type III		
3-Methylglutaconic aciduria	Carnitine/acylcarnitine translocase deficiency	Defects of biopterin cofactor regeneration		
	Carnitine palmitoyltransferase Ia deficiency (L)	Hypermethioninemia		
	Dienoyl-CoA reductase deficiency	Citrullinemia type II		

Abbreviations: Cbl indicates cobalamin; Hb, hemoglobin.

Maternal and Child Health Bureau. Newborn screening: toward a uniform screening panel and system. Executive summary. Rockville (MD): MCHB; 2005. Available at: <http://mchb.hrsa.gov/screening/summary.htm>. Retrieved September 10, 2007.

globinopathies that uses isoelectric focusing, high-performance liquid chromatography, or electrophoresis, 3) screening for hearing loss that incorporates either otoacoustic emissions or auditory brainstem response, and 4) screening for infectious diseases (eg, human immunodeficiency virus [HIV] and toxoplasmosis) using immuno-

assays for disease specific immunoglobulin G and immunoglobulin M antibodies.

Newborn screening programs are expected to operate with maximal sensitivity and specificity within a public health model that must account for population-based challenges that are distinct from the more familiar chal-

lenges of a single-patient diagnosis. There are at least eight different testing platforms used in screening for the 29 conditions listed in Table 1 (eg, MS/MS screens for 22 of the listed conditions). Although patients may inquire regarding the detection rate (sensitivity) and the positive predictive value, these data are not readily available for the aggregate of tests. Performance data for specific screening tests or platforms require discussions with the state screening laboratory. State-specific contact information for newborn screening programs can be found at the web site of the National Newborn Screening and Genetics Resource Center (<http://genes-r-us.uthscsa.edu>).

Statistical uncertainty is driven in large part by the addition of MS/MS technology used to screen for rare metabolic conditions (Table 1). With any technology, the rate of false-positive results are reduced as experience grows (5). Defining detection rates using MS/MS is complicated by incomplete data reporting, variation in testing procedures, variation in definition of false-positive results, variation in case definition, and nonuniform screening thresholds. Calculating detection rates is made difficult by the nature of the disorders being screened for and the inability to determine prevalence with confidence. For example, it is not uncommon for children with rare metabolic disorders to succumb before a diagnosis can be made. These aspects are compounded by the problems commonly encountered in clinical laboratory settings, including inadequate clinical information and mislabeled samples. Performance goals for newborn screening using MS/MS have been suggested (6). On average, the number of neonates that must be tested to detect one affected patient should be approximately 3,000. A performance goal is used to ensure that at least one fifth of patients (20%) with a positive screening result will, after follow-up testing, be determined to be affected (positive predictive value). Finally, by addressing causes of false-positive rates, these may be reduced to approximately 3 per 1,000 results. These screening test performance goals compare with first-trimester screening for aneuploidy as follows: 1) at least 6–7 individuals per 3,000 screened individuals are affected, 2) the positive predictive value for patients aged 35 years is approximately 4–5%, 3) the false-positive rate for first trimester screening is approximately 5% for women younger than 35 years at the time of delivery (7–9).

Each state program must have a system in place for notification, timely follow-up, and evaluation of any infant with a positive screening result. Furthermore, the system should incorporate protocols for more evaluation, treatment, and long-term follow-up for any infant whose positive screening result suggests a likely risk of the condition. Positive newborn screening results typically are reported to the newborn's primary care provider and, subsequently, the custodial parent(s).

Patients typically are not billed for their participation in newborn screening programs. Newborn screening is mandated by state statute or regulation, and, in most states,

parents are informed that testing will be done as part of standard care unless they specifically decline ("opt out" consent process); Maryland, the District of Columbia, and Wyoming currently require written consent ("opt in"). Many states allow parents to refuse testing based on religious or personal grounds. Hospitals and newborn nurseries usually provide written materials to parents immediately postpartum to inform them of the newborn screening their children will undergo. Survey data suggest that patients are underinformed regarding newborn screening (10) and desire information during the prenatal period. Prenatal education about newborn screening not only provides parents with the reasons for obtaining their newborn's blood specimen, but also informs them that an initial positive test result does not necessarily mean that their child has the condition for which the screening result was positive. Materials are available on the web site of the American College of Obstetricians and Gynecologists ([http://www.acog.org/from\\_home/misc/dept\\_pubs.cfm](http://www.acog.org/from_home/misc/dept_pubs.cfm)).

Newborn screening programs have enormous public health benefits and have been effective in identifying newborns that can benefit from early treatment. In addition, many couples have been made aware of their carrier status because of diagnoses in their newborns. There are many important issues surrounding the debate on universal screening, including financial resources, level of screening, continuity of care, and informed consent. To date, policy on newborn screening has been fragmented, but efforts are underway to ensure uniformity and equity for all newborns. Obstetrician–gynecologists are encouraged to make written or video materials or electronic information available to parents regarding the availability of newborn screening tests.

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