Clinical Expert Series

CME

Newborn Screening and the Obstetrician

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Newborn screening is the largest genetic screening program in the United States with approximately four million newborns screened yearly. It has been available and in continuous development for more than 50 years. Each state manages, funds, and maintains its own individual program, which encompasses newborn screening as well as the diagnosis and coordination of care for affected infants and children. The ideal disorder for screening is one in which newborn intervention prevents later disabilities or death for infants who may appear normal at birth. There are 31 core conditions that are currently recommended for incorporation into state screening programs. To obtain a sample, several drops of blood are collected from the newborn's heel and applied to filter paper. Although testing for core disorders is fairly standardized, more extensive screening varies by state and the rigorous evaluation of new disorders for inclusion in state screening panels is ongoing. As genomic medicine becomes more accessible, screening newborns for chronic diseases that may affect their long-term health will need to be addressed as well as the use of the residual blood spots for research. Obstetric providers should, at some time during pregnancy, review the basic process of newborn screening with parents to prepare them for this testing in the neonatal period. This information can be reviewed as it best suits incorporation in an individual's practice; verbal discussion and the distribution of written materials with resources for further information are encouraged.

(Obstet Gynecol 2012;120:908–17)
DOI: http://10.1097/AOG.0b013e31826b2f03

Newborn screening is a mandated public health program designed for the identification of disorders in which early intervention improves long-term health outcomes in children. It is the largest genetic screening program in the United States with approximately four million newborns screened yearly. It is designed to provide rapid diagnosis and allow early therapy for specific metabolic, infectious, and other genetic disorders for which early intervention reduces disabilities and death. This important practice typically occurs before the development of signs or symptoms of disease. Newborn screening programs are comprised of a complex, integrated clinical service of education, screening, diagnosis, follow-up, evaluation, and often, long-term management. When a newborn screen is found to be positive, confirmatory diagnostic testing and subsequent pediatric care are coordinated and provided for through the screening program. Once a treatment plan has been developed for an affected newborn, and if there is medical compliance, most newborns will have normal development.

With more than 4 million newborns screened each year, newborn screening is the most common form of genetic testing in the United States, performed in 51 programs in the United States (50 states as well as the District of Columbia). Newborn screening identifies approximately 6,000 newborns each year who are found to have a serious condition for which treatment can dramatically improve their lives.[1] In addition, more than 12,000 newborns are found to have a hearing deficiency for which early intervention will improve their outcomes.[2] Although

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Continuing medical education for this article is available at http://links.lww.com/AOG/A320.

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Financial Disclosure
The authors did not report any potential conflicts of interest.

ISSN: 0029-7844/12

the individual risk to a newborn for one of these disorders is rare, the combined incidence of disease for all of the screened disorders by blood sampling is estimated to be as high as 1:500–1:1,000 births.[1] The success of newborn screening in improving neonatal and childhood health has prompted the expansion of newborn screening programs over the past 10 years.

Given that newborn screening typically occurs while the mother is immediately postpartum, obstetricians and health care providers caring for women during this critical time are uniquely positioned to give basic information to women before delivery and to answer questions during the antenatal and postpartum period. Davis and colleagues[3] used focus groups to evaluate what parents wanted to understand about newborn screening and identified seven points essential to simplifying information about this program to parents (Box 1). Indeed, the recent American College of Obstetricians and Gynecologists Committee Opinion on Newborn Screening,[4] the federal Human Resources and Service Administration,[5] the American College of Medical Genetics,[6] and the American Academy of Pediatrics[7] all emphasize that communication about newborn screening at some time during prenatal care is strongly recommended as an important clinical practice.

Box 1. 7 Things Parents Want to Know About Newborn Screening*

1. All newborn babies are required by the State to get tested for some rare disorders before they leave the hospital.
2. Babies with these disorders may look healthy at birth.
3. Serious problems can be prevented if we find out about the disorders right away.
4. To do the test, a nurse will take a few drops of blood from your baby's heel.
5. Your baby's health professional and hospital will get a copy of the test results. Ask about the results when you see your baby's health professional.
6. Some babies will need to be retested. If your baby needs to be retested you will be notified. It is very important to get retested quickly.
7. Talk to your baby's health professional if you have questions.

* National Newborn Screening and Genetics Resource Center and Department of Pediatrics, University of Texas Health Science Center at San Antonio. 7 Things Parents Want to Know About Newborn Screening. Reprinted with permission.

HISTORY

Newborn screening was initiated more than 50 years ago by Dr. Robert Guthrie of New York State when he developed a simple blood test to detect elevated levels of phenylalanine in newborns with phenylketonuria. Phenylketonuria is an autosomal-recessive metabolic condition in which individuals lack the hepatic enzyme phenylalanine hydroxylase and develop elevated levels of phenylalanine causing seizures and significant developmental delay. The blood test used for detection of phenylketonuria, a bacteria inhibition assay, relied on the finding that high phenylalanine levels prevented bacteria from growing. If a diagnosis was made through this test, mental retardation could be avoided by placing affected newborns on a special diet lacking phenylalanine. Newborn screening for phenylketonuria was subsequently instituted in all 50 states and the District of Columbia in the 1960s. The success of phenylketonuria screening established the basis for all forms of newborn screening. Specifically, it met the original criteria for screening for inborn errors of metabolism set forth by Wilson and Jungner in 1968 (Box 2).[8] States have added additional conditions to their newborn screen-

Box 2. Principles of Early-Disease Detection

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic state.
5. There should be a suitable test or examination.
6. The test or examination should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a "once and for all" project.

Reprinted from Wilson JMG, Jungner G. Principles and practice of screening for disease (public papers no. 34). Geneva (Switzerland): World Health Organization; 1968.

ing panels based on these criteria, including congenital hypothyroidism, congenital adrenal hyperplasia, homocystinuria, galactosemia, maple syrup urine disease, biotinidase deficiency, and hemoglobinopathies such as sickle cell anemia.

In 2002, most states were screening for eight disorders or less; by the early 2000s, newborn screening programs in the United States were pressured to expand as a result of advances in technology and medical therapy. Although newborn screening had traditionally focused on metabolic conditions, scientific and clinical developments allowed the addition of other types of genetic diseases such as cystic fibrosis (CF). The widespread use of tandem mass spectrometry, a sophisticated instrument to rapidly identify specific metabolic compounds, now provides more accurate screening for aminoacidopathies such as phenylketonuria and allowed expanded newborn screening for fatty acid oxidation disorders such as medium chain acyl-coA dehydrogenase deficiency and organic acid disorders such as glutaric academia type I. In addition, technologic advancements in testing for newborn hearing deficits prompted the inclusion of newborn hearing screening in many states.

In the past, there had been significant variation in screening; some states were screening for one or two conditions, whereas others were screening for 10 diseases or more. This variation did not provide equity in access to care for newborns, and advocacy organizations eventually called for a uniform panel of conditions. Stakeholders in the process included consumer advocacy groups, parent groups representing children affected by diseases under consideration for screening, public health agencies, legislative bodies, and voluntary health organizations. In 2002, the Maternal and Child Health Bureau of the Health Resources and Services Administration of the U.S. Department of Health and Human Services commissioned the American College of Medical Genetics to develop recommendations regarding the development of a uniform panel of conditions for newborn screening. The report, "Newborn Screening: Toward a Uniform Screening Panel and System," issued in 2005[9] and published in 2006,[6] recommended 29 core conditions for which all newborns born in the United States should receive screening. Efforts to expand the screening panel were enhanced by the Newborn Screening Saves Lives Act of 2008, authorizing funding to states to strengthen their newborn screening programs. The Secretary's Advisory Committee on Heritable Disorders in Newborns and Children was chartered in 2003 to review standards and develop policies for reducing morbidity and mortality in newborns and children who have or who are at risk for serious heritable disorders. This Committee advises the Secretary of the U.S. Department of Health and Human Services on the most appropriate application of newborn screening. Advised by the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children, the U.S. Department of Health and Human Services Secretary endorsed the uniform panel and states began to adopt it, many expanding their list of conditions screened to 29 or more (Box 3).[10] For each condition in the core uniform panel, effective treatment is available. The report from the American College of Medical Genetics also identified 20 additional secondary conditions for which testing is available but for which there are no known effective treatments. These conditions are not recommended as core screening conditions; however, if testing is performed, the results of these conditions should be reported.

CHOOSING CONDITIONS FOR STATE NEWBORN SCREENING PANELS

There is a rigorous process for including conditions in the newborn screening core panel. Since 2007, nine conditions have been proposed to the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children for inclusion on the panel. After extensive evaluation, two new disorders have ultimately been recommended as additions to the core panel for screening: severe combined immunodeficiency and critical congenital heart disease. With the addition of severe combined immunodeficiency in May 2011, 30 conditions comprise the core panel for screening. Currently, data are being collected on the 31st condition, critical congenital heart disease, in anticipation of its addition to the core panel. As a result of these efforts in newborn screening, all states presently screen for at least 26 conditions and some states screen for 50 or more diseases.

Authority for determining what constitutes a state's panel generally includes the state health department or its board of health with advice from an advisory committee. These groups consider the prevalence of the disorder in their population as well as the cost of implementing a new test and subsequent medical protocols. State programs assign screening cutoffs defining the threshold for both screen-positive and screen-negative test results for each condition on their newborn screening panel seeking advice from their advisory committee when defining the optimal screening threshold for each condition. To do so, they must take into account the prevalence of each condi-

Box 3. Newborn Screening Panel: Core Panel

Inborn Errors of Organic Acid Metabolism

Isovaleric acidemia
Glutaric acidemia type 1
3-hydroxy 3-methyl glutaric aciduria
Holocarboxylase deficiency
Methylmalonic acidemia (mutase)
3-methylcrotonyl-CoA carboxylase deficiency
Methylmalonic acidemia (Cbl A, B)
Propionic acidemia
b-Ketothiolase deficiency

Inborn Errors of Fatty Acid Metabolism

Medium-chain acyl-CoA dehydrogenase deficiency
Very long-chain acyl-CoA dehydrogenase deficiency
Long-chain 3-OH acyl-CoA dehydrogenase deficiency
Trifunctional protein deficiency
Carnitine uptake/transport defect

Inborn Errors of Amino Acid Metabolism

Phenylketonuria
Maple syrup urine disease
Homocystinuria
Citrullinemia type I
Argininosuccinic acidemia
Tyrosinemia type I

Hemoglobinopathies

Hb SS disease (sickle cell anemia)
Hb S/beta-thalassemia-thalassemia
Hb S/C disease

Miscellaneous Multisystem Disease

Primary congenital hypothyroidism
Biotinidase deficiency
Congenital adrenal hyperplasia
Classic galactosemia
Cystic fibrosis
Severe combined immunodeficiency

Newborn Screening Methods Other Than Blood Testing

Congenital hearing loss

Data from Secretary's Advisory Committee on Heritable Disorders in Newborns and Children. Recommended uniform screening panel of the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children. Available at: www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/recommendedpanel/index.html. Retrieved March 19, 2012.

tion, which may vary between states. Also, they must consider the effect of a very sensitive test cutoff, which will identify most affected children but also have a high false-positive rate. All positive screening tests require counseling and follow-up testing to confirm that the child is affected. False-positive results add to the burden of screening programs by increasing the financial burden as well as causing significant parental anxiety. At the same time, false-negative test results have to be minimized, because they will inaccurately report that affected children are free of disease, delaying their eventual diagnosis, and, in many cases, worsening the child's outcome.

THE PROCESS AND STANDARDIZATION OF NEWBORN SCREENING

Aside from standardization of how newborn screening samples are obtained on filter paper and processed,[11] there are no national guidelines for newborn screening. Although all states have legislation to ensure a newborn screening program, states vary with regard to what conditions for which they screen. Each state is responsible for developing and maintaining its own program. Therefore, each state develops a complex interaction among the laboratory, public health program, pediatricians, subspecialists, and specialty care centers depending on the available resources. They must ensure communication of the initial positive test, referral for repeat screening, diagnostic assessment and testing, or both, genetic counseling about the inheritance of the disorder (if applicable), and arrange follow-up care and long-term resources. Initial testing is performed by obtaining a sample of the newborn's blood by a tiny heel prick, which is placed on special filter paper and is sent to the laboratory within 24 hours. Newborns who are sick, premature, require parenteral nutrition or blood transfusions, or deliver outside of the hospital setting may undergo newborn screening on a more variable timeframe. The diseases on the screening panel as well as the protocols for management of a screen-positive test are determined by individual state health departments. In 2009, the fees charged per newborn screen ranged up to $125.00 with several states having no fees associated with their programs.[12] For those newborns with a positive newborn screen, the cost of diagnostic testing and follow-up care is additional.

The Centers for Disease Control and Prevention and Human Resources and Service Administration monitor screening programs. All state laboratories participate in the Newborn Screening Quality Assurance Program. The Newborn Screening Quality Assurance Program is part of the Newborn Screening

and Molecular Biology Branch of the Centers for Disease Control and Prevention operated in partnership with the Association of Public Health Laboratories. It is a voluntary program intended to help state health departments and laboratories maintain test result quality. The program provides training, guidelines, consultation, and proficiency testing and reference materials for laboratories. The quality control and proficiency testing program prepares and distributes to laboratories more than 700,000 dried blood spots per year for proficiency testing and quality performance review.[13]

CONDITIONS EVALUATED IN NEWBORN SCREENING PROGRAMS

Developments in technology and in genomic medicine have increased the ability to screen for large numbers of genetic disorders. Multiple technologies are used on the dried blood spots including tandem mass spectrometry, real-time polymerase chain reactions, electrophoresis, and enzyme assays. A test is currently in development to screen for critical congenital heart disease with newborn pulse oximetry measurements in the hospital setting.

Although the original focus of newborn screening was on conditions that affect the central nervous system, the core panel now tests for five main categories of disorders: 1) disorders of amino acid metabolism; 2) disorders of organic acid metabolism; 3) fatty acid oxidation disorders; 4) hemoglobinopathies; and 5) a group of assorted other conditions, including hearing screening. Tandem mass spectrometry is used to test for disorders of amino acids, fatty acids, and organic acids. High-performance liquid chromatography is often used to test for several different types of hemoglobinopathies, and a variety of other techniques are used to test for other main conditions.

Amino Acid Disorders

Amino acid disorders are inherited metabolic disorders, which, as a result of an interruption of amino acid metabolism, cause a build-up of toxins. General symptoms of amino acid disorders include poor feeding, lethargy, hypotonia, seizures, mental retardation and developmental regression, unusual odors, and growth failure. Treatment generally consists of medications as well as a low-protein diet. Most of these disorders are autosomal-recessive and are therefore unlikely to be identified by a family history. An example of such a disorder would be phenylketonuria. The incidence of these disorders range from 1:25,000 (phenylketonuria) to 1:100,000 (maple syrup urine disease, citrullinemia, tyrosinemia type 1, among others).

Organic Acid Disorders

Organic acid disorders are each associated with a specific enzyme deficiency, which leads to an accumulation of blood levels of the specific organic acid. These disorders have a variable age of onset depending on the condition. Increased levels of organic acids can cause lethargy, failure to thrive, vomiting, seizures, developmental delay, and coma. Most require specific protein restrictions and nutritional supplements. Propionic acidemia would be an example of such a disorder. Most are autosomal-recessive in inheritance and are therefore unlikely to be identified in a family prenatally. The incidence of these ranges from 1:75,000 to 1:100,000.

Fatty Acid Disorders

Fatty acid disorders are inherited metabolic conditions that decrease energy metabolism as a result of an accumulation of fatty acid metabolites; affected individuals have an impaired ability to metabolize fats. Specific enzymes such as medium chain acyl co-A dehydrogenase deficiency affect the fatty acid metabolic pathway. The classic clinical presentation of children with these disorders is one of an apparently healthy child who, when undergoing periods of prolonged fasting or increased energy demands, develops unexplained lethargy, vomiting, and seizures and becomes nonresponsive. Affected children require regular feeding to avoid periods of relative starvation because they have an impaired ability to metabolize fats. Most fatty acid disorders have an autosomal-recessive inheritance pattern. Therefore, it is unlikely that a family history (unless consanguineous) would identify these disorders within a family. The incidence ranges from 1:25,000 to 1:100,000.

Hemoglobinopathies

Hemoglobinopathies are relatively common conditions with variable severity, ranging from mild anemias to damage to organ systems, infections, and significant pain. They may be the result of structural abnormalities in the hemoglobin molecule in disorders such as sickle cell anemia. The clinical manifestations may also be caused by an inadequate production of hemoglobin caused by α-thalassemia. Although the thalassemias are classically found to be most common in those of Mediterranean, Asian, African, or Indian descent, given the increasing presentation of admixed populations from various racial and ethnic groups, these disorders can be identified in

all ethnic groups. Therapies may include support for persistent anemias including blood transfusions, pain management, prophylactic antibiotics, vaccinations such as Pneumovax for those with sickle cell anemia, and medical screenings to assess end-organ damage resulting from these disorders. Most have autosomal-recessive inheritance. The incidence ranges vary greatly depending on the disorder and ethnicity. For example, the risk for sickle cell disease ranges from 1:400 for those of African American descent to 1:5,000 for those of other ethnic backgrounds.

Miscellaneous Disorders in Newborn Screening

Cystic Fibrosis

After sickle cell anemia, CF is the second most common inherited life-shortening disease of childhood onset in the United States. Treatment depends on the severity of presentation, which is highly variable. The severe manifestations of CF include pulmonary disease, failure to thrive, and pancreatic insufficiency. Milder forms can present as male infertility with congenital bilateral absence of the vas deferens or nasal polyps. Patients with CF have mutations in the CF transmembrane conductance regulator gene found on chromosome 7. Although the incidence of CF differs by ethnicity (given that different mutations segregate with varying ethnic groups), the overall birth prevalence of CF in the United States is approximately 1:3,500 births.[14] All women who present for preconception or prenatal care should be offered screening for CF.[15] Current standards suggest that a panel of at least 23 mutations be used for CF screening during pregnancy.[16]

Newborn screening evaluates functional defects in the CF protein by initiating screening with immunoreactive trypsinogen concentrations. Immunoreactive trypsinogen levels are elevated in children with CF, presumably from the leaking of this protein into the circulation after exocrine pancreatic injury. If an initial immunoreactive trypsinogen level is elevated, some states repeat the dried blood spot test in 2–3 weeks from the original sample; most others perform mutation analysis from the blood spot for a set of CF mutations common to the ethnic groups in their individual state. In programs that perform mutation analysis, two mutations identified on the bloodspot confirm the diagnosis of CF. If only one mutation is identified, the child is sent for a sweat test as the definitive assessment for CF, because the second mutation may not be identified by the state's panel. For states that perform two immunoreactive trypsinogen tests, sweat testing is also the definitive confirmatory test. Sweat testing can be reliably performed after 1 week of life. Currently, a sweat chloride level of 60 mmol/L is diagnostic of CF; a value ranging from 30 mmol/L to59 mmol/L is a borderline result that requires a repeat test, DNA analysis (if not previously performed), or both. Approximately 5% of individuals will have persistent borderline sweat tests and it is unclear what the long-term outcome is for these individuals. Newborns with CF who have pancreatic insufficiency in the first few weeks of life are at risk of severe nutritional complications. Pancreatic enzyme replacement therapy, fat-soluble vitamin supplements, and salt replacement are initiated immediately after the diagnosis is made in pancreatic-insufficient patients. Additional therapy relates to symptoms and presentation but may include nutritional supplementation, pulmonary therapy, antibiotics, and enzyme replacement for pancreatic disorders. Cystic fibrosis is inherited in an autosomal-recessive manner.

Biotinidase Deficiency

Biotinidase deficiency prevents the recycling of the vitamin biotin. It can result in seizures, infections, hearing loss, and mental retardation; if untreated, it can result in coma and death. Treatment with daily biotin supplementation completely prevents these symptoms. The inheritance pattern is autosomal-recessive with an incidence of greater than 1:75,000 births.

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia can be caused by various enzyme deficiencies. The most common form is the result of an enzyme deficiency of 21 hydroxylase, which results in impaired adrenal synthesis of cortisol from cholesterol. The salt-wasting form of 21 hydroxylase deficiency has an incidence of 1:15,000 live births. This form causes fetal virilization in affected female fetuses. Virilization of the genetically female fetus often results in ambiguous genitalia; excess androgens do not produce anatomic changes in male offspring. Because newborns with the salt-wasting form can have life-threatening salt-wasting crises, rapid identification of the 21-hydroxylase form through newborn screening is essential. Management includes glucocorticoid replacement as well as management of the virilized female. All forms are inherited as autosomal-recessive conditions; the incidence is greater than 1:25,000 births for all forms of this enzyme disorder.

Congenital Hypothyroidism

Congenital hypothyroidism may result from an absent thyroid gland or from failure of the thyroid to either develop or function properly. It can cause severe growth delay and mental retardation as a result of inadequate or absent thyroid hormone in the newborn. Therapy requires lifelong thyroid replacement, which can be taken orally. If treatment begins within the first month of life, development is usually normal. Although most cases are sporadic, approximately 20% of these are inherited, mostly in an autosomal-recessive manner; some autosomal-dominant cases have been described. The incidence is estimated at greater than 1:5,000 births.

Galactosemia

Galactosemia is caused by a deficiency in the galactose-1 phosphate uridyltransferase enzyme, which results in impaired galactose metabolism. This liver enzyme is needed to convert galactose into glucose for energy metabolism. The accumulation of galactose causes the clinical presentation of failure to thrive, infection, cataracts, liver failure, mental retardation, and death. Dietary intervention is designed to restrict galactose and has variable outcomes.

A milder presentation of galactosemia is known as the "Duarte variant," which is often but not always detected by newborn screening. These children may have no sequelae or have milder findings than the severe form of galactosemia; treatment for this form is controversial. Both types have an autosomal-recessive inheritance pattern; the incidence is greater than 1:30,000 births for classic galactosemia and approximately 1:16,000 for the Duarte variant.[17]

Hearing

If undetected at birth, hearing impairment can affect speech and language acquisition, emotional and social development, and academic achievement. Without newborn hearing screening, most children are not identified as hearing-impaired until 2–3 years of age. The number of newborns born with significant permanent hearing loss is estimated at one to three per 1,000 with an estimated three per 1,000 with moderate hearing loss.[18] Newborn hearing screening is typically performed by evoked otoacoustic emissions or by the auditory brain stem response measures. Otoacoustic emissions are designed to measure the cochlea's response to sound. To perform the test, a small probe is placed in the newborn's ear, sounds are introduced, and the response is recorded; if no response is noted, the newborn may have a hearing deficiency. To obtain auditory brain stem response measures, three surface electrodes are placed on the forehead, nape, and mastoid to detect waveforms recorded from stimuli given at 35 dB. The waveforms generated are compared with a standard. Delayed or absent waves are suggestive of a neurologic or cochlear defect. Newborn hearing screening defines permanent unilateral or bilateral hearing loss as 30–40 dB hearing level or greater across the frequencies of 500–40,000 Hz, which is the range that is essential for speech recognition and comprehension. Newborns who fail either screening test are referred for additional audiologic evaluation.

Severe Combined Immunodeficiency

Severe combined immunodeficiency is a primary immune deficiency syndrome with a severe defect in both the T and B lymphocytes. It causes an increased susceptibility to a variety of infections as well as failure to thrive. Children with untreated severe combined immunodeficiency have a life expectancy of approximately 2 years. Treatment consists mainly of early bone marrow transplant. It is the first newborn screening disorder that is DNA-based for identification. Currently approximately eight states screen for severe combined immunodeficiency; seven states have testing required by their state but have not yet implemented screening.[19] Although it has been recommended as an addition to the core panel of screened disorders, it may be several years before it is adopted nationally. There are several forms of this disorder; it is most commonly inherited as an autosomal-recessive condition but also occurs with X-linked inheritance. The incidence is greater than 1:100,000 live births.[20]

Critical Congenital Heart Disease

Congenital heart disease affects approximately 8:1,000 newborns and accounts for 24% of all infant deaths resulting from congenital birth defects.[21] The subgroup of critical congenital heart disease is defined as heart disease with a severe, life-threatening presentation within the first year of life and is composed of seven conditions: tetralogy of Fallot, hypoplastic left heart syndrome, pulmonary atresia (with intact septum), total anomalous pulmonary venous return, transposition of the great arteries, tricuspid atresia, and truncus arteriosus. In September, 2010, the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children voted to add critical congenital heart disease to the core panel, recommending the use of pulse oximetry to identify critical congenital heart disease in newborns. The noninva-

sive pulse oximetry evaluation measures the percent of hemoglobin oxygen saturation and is a technique that is readily available and could be implemented in all newborn nurseries. Although this recommendation has been made, the committee also suggested that evaluation of protocols for implementation of the screening test and demonstration of improved health outcomes will need to be performed and that Health Resources and Services Administration should guide screening standards and infrastructure for this program. As of February 2012, only New Jersey was screening for critical congenital heart disease.[19]

ETHICAL, LEGAL, AND SOCIAL ISSUES

The medical screening and diagnostic testing of minors raises the consideration of substantial ethical, legal, and social concerns. Among these are issues regarding the benefits and risks of screening, the identification and management of both primary and secondary diseases (or targets), the psychological effect of false-positive screening results, the potential expansion of screening for adult disease with more advanced genetic testing, consent requirements, the use of residual blood spots for research, and educational requirements as newborn screening expands and adopts new technologies.[22,23]

The original criteria for adding a condition to newborn screening panels suggested that an immediate, life-saving intervention needed to be available to warrant screening. This assumption has been challenged, and some groups have suggested a broader consideration of benefits.[24] Secondary targets, which are conditions that can be easily identified by tandem mass spectrometry but for which no known therapies exist, generate complex issues. It has been suggested that providing such information adds stress and anxiety to parents without providing a benefit. Others have suggested that newborn screening for these secondary target disorders can help families avert a "diagnostic odyssey" during which they spend much of early childhood visiting one doctor after another trying to achieve a diagnosis for a symptomatic child with a rare disease. Some families have argued that they would like to know any information about their newborn that is available, regardless of its clinical use. In addition, identifying secondary targets for which there are currently no known treatments can allow families to enroll their newborns in studies that can define the natural history of these conditions and potentially lead to therapies.[25]

Consideration of whether newborn screening results should support only the newborn, or whether benefits to parents or siblings should be considered, is also a controversial issue. Identifying a newborn with an autosomal-recessive condition demonstrates the carrier state of both parents and provides valuable information for reproductive planning, which is often explained by a genetic counselor. How to balance the benefits to the newborn and the benefits to parents and potential future siblings is not known.

As next-generation sequencing becomes more efficient and less expensive, every newborn's entire genome sequence potentially could be available within 1 week of birth. How this information should be identified and reported will need to be determined.[26] Newborn screening will therefore have the ability to screen for adult-onset conditions. For example, although there is no immediate need for a family to know that their newborn is a carrier of a *BRCA1* or *BRCA2* mutation associated with familial breast and ovarian cancer syndrome, testing a newborn is technically possible. Currently, these types of targets have not been considered for newborn screening; however, genetic predisposition to childhood-onset conditions such as multiple endocrine neoplasia type 2 may challenge this position when interventions during childhood such as prophylactic thyroidectomy have been shown to be lifesaving.

False-positive test results are part of every screening program and, as programs expand to test for more conditions, more false-positive test results will be reported. Given the emotional nature of the newborn period, many women and families report lasting negative effects of false-positive test results, including decreased bonding and parental stress associated with the newborn and continued testing and treatment of the child, even when the diagnostic testing is negative.[24] This raises the question as to whether it would be better to integrate some testing into pediatric care (at 6 months of age perhaps) rather than on the second day of life.

Each state's newborn screening laboratory handles the management of residual blood spots independently. The blood spots capture a population-based DNA registry for each state and represent a vast opportunity for research. However, this raises concerns about parental consent for research and the ability to opt in or out of research.[27] Some states such as Texas and Minnesota have experienced legal challenges and have opted to destroy blood spots after newborn screening is completed. Others such as Michigan have undertaken a parental engagement process, which has garnered support for research on residual blood spots as long as parents had a choice about participation and robust oversight mechanisms are in place.[28]

The success of newborn screening has led to unanticipated consequences for obstetricians as the

first generation of individuals who benefited from newborn screening enter their reproductive years. Newborns who were diagnosed with phenylketonuria and adhered to phenylalanine-free diets have led healthy lives and many relax their dietary restriction in late adolescence and adulthood. However, once a woman with phenylketonuria is planning a pregnancy or becomes pregnant, it is essential that she continue her strict phenylalanine-free diet so that her developing fetus does not suffer the neurologic consequences of elevated maternal phenylalanine levels. Identifying women with phenylketonuria and providing them with guidance during preconception care as well as offering carrier screening to their partners to determine their risk for an affected child are important roles for specialty obstetric and genetic services.[29]

NEWBORN SCREENING AND THE ROLE OF THE OBSTETRICIAN

Because newborn screening typically occurs during the newborn's hospital stay before discharge, obstetric care providers are in a unique position to inform parents during pregnancy about this important health initiative. Given the emotional nature of the postpartum period, the prenatal period is a better time for education. Although health care providers have different practice styles, times to discuss newborn screening should coincide with other educational discussions regarding obstetric care. This might include the first prenatal visit, the midtrimester discussion regarding glucose screening for diabetes, or the third-trimester visit when performing group B streptococcal screening and discussing delivery planning. In March 2011, the American College of Obstetrics and Gynecologists published a Committee Opinion on newborn screening, which recommends educating parents about newborn screening before birth at any time during the prenatal period.[4] It lists resources for both health care providers and patients to make information about newborn screening easily accessible. This recommendation is based on prior evidence from focus groups and surveys that women and their families wish to understand newborn screening before delivery.[3,30] Given that health information regarding specific newborn screening diseases is difficult to understand, simple brochures explaining the process are essential.

CONCLUSION: CURRENT AND FUTURE CHALLENGES

Public health departments must continue to maintain newborn screening programs, to integrate all aspects of care from screening to medical therapy, and to introduce new screening tests. Advances in genomic medicine have the capacity to shift the focus of newborn screening away from the diagnoses that need immediate intervention and toward the screening of newborns for disorders that affect long-term health such as the propensity to develop coronary artery disease or some forms of cancer. This will cause significant organizational and financial stresses and may require a reassessment of the goals of newborn screening and complex evaluation and planning before implementation.

There are critical shortages of experts in the clinical assessment and long-term management for many of these rare disorders. Families may have to travel long distances to undergo diagnostic testing after an initial positive screen or to receive specialized medical care on a regular basis. Limited long-term data on health outcomes for many of these disorders are available, and there is no uniform mechanism for evaluation of outcomes. The management of false-positive testing continues to be challenging for screening programs. Given the stress placed on families with false-positive screens, minimizing false-positive tests is important as new tests are being considered for inclusion. Furthermore, some children are not screened, either as a result of issues of illness or home birth or as a result of parents' refusal to screen their newborn for religious considerations, which is allowed in many states.

Finally, although this is a broad public health program, there is limited public awareness about the value of newborn screening.[31] The American College of Medical Genetics has determined that September is National Newborn Screening Awareness Month to improve understanding about this important genetics health initiative. Obstetric providers have an essential role in the success of newborn screening by informing pregnant women about this important public health program before delivery.

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