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Newborn Screening and the Obstetrician

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Abstract

Newborn screening is the largest genetic screening program in the United States, with approximately four million infants screened yearly. It has been available and in continuous development for over 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 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 is encouraged.

Introduction

Newborn screening (NBS) 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 infants 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 prior to 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

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been developed for an affected child, and if there is medical compliance, most newborns will have normal development.

With over four million infants screened each year, NBS 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 babies 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 the individual risk to an infant 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 1:500–1:1000 births.¹ The success of newborn screening in improving neonatal and childhood health has prompted the expansion of newborn screening programs over the past ten years.

Given that newborn screening typically occurs while the mother is immediately postpartum, obstetricians and 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 used focus groups to evaluate what parents wanted to understand about NBS, and identified seven points essential to simplifying information about this program to parents (Box 1).³ Indeed, the recent American College of Obstetricians and Gynecologists Committee Opinion on Newborn Screening⁴, the federal Human Resources and Service Administration (HRSA),⁵ the American College of Medical Genetics (ACMG)⁶, and the American Academy of Pediatrics,⁷ all emphasize that communication about NBS 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.

History

Newborn screening was initiated over fifty 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 (PKU). PKU is an autosomal recessive metabolic condition

*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.

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 PKU, 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 PKU was subsequently instituted in all 50 states and the District of Columbia in the 1960's. The success of PKU 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 screening 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.

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: World Health Organization, 1968.

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 due to 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 PKU and allowed expanded newborn screening for fatty acid oxidation disorders such as medium chain acyl-coA dehydrogenase deficiency (MCADD) 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 while others were screening for ten 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 (HRSA) of the United States Department of Health and Human Services (DHHS) 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 2005⁹ and published in 2006⁶, 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 (SACHDNC) 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 United States Department of Health and Human Services (DHHS) on the most appropriate application of newborn screening. Advised by the SACHDNC, the DHHS 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 ACMG 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.

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: <http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/recommendedpanel/index.html>. Retrieved March 19, 2012.

Choosing conditions for State Newborn Screening Panels

There is a rigorous process for including conditions in the NBS core panel. Since 2007, nine conditions have been proposed to the SACHDNC 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 (SCID) and critical congenital heart disease (CCHD). With the addition of SCID in May 2011, 30 conditions comprise the core panel for screening. Currently, data are being collected on the 31st condition, critical congenital heart disease (CCHD), 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 cut-offs 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 condition, which may vary between states. Also, they must consider the impact 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, since 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 NBS. 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 between 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 and/or diagnostic assessment and testing, 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. Infants that are sick, premature, require parenteral nutrition, 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 infants with a positive newborn screen, the cost of diagnostic testing and follow up care is additional.

The Centers for Disease Control (CDC) and HRSA monitor screening programs. All state laboratories participate in the NSQAP (Newborn Screening Quality Assurance Program). The NSQAP is part of the Newborn Screening and Molecular Biology Branch of the CDC 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 NBS 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, due to 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 (MSUD, 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 range from 1:75,000 to 1:100,000.

Fatty Acid Disorders

Fatty acid disorders are inherited metabolic conditions that decrease energy metabolism due to 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, develop unexplained lethargy, vomiting, seizures, and become non-responsive. Affected children require regular feeding to avoid periods of relative starvation since 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 1:25,000–1:100,000.

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 due to 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 alpha 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 due to 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, cystic fibrosis (CF) is the second most common inherited life shortening disease of childhood onset in the United States. Treatment depends upon 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 (CBAVD) or nasal polyps. Patients with CF have mutations in the cystic fibrosis transmembrane conductance regulator gene (CFTR) 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 about 1:3500 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 a 23 mutations be used for CF screening during pregnancy¹⁶.

Newborn screening evaluates functional defects in the CF protein by initiating screening with immunoreactive trypsinogen (IRT) concentrations. IRT levels are elevated in children with CF, presumably from the leaking of this protein into the circulation after exocrine pancreatic injury. If an initial IRT 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, since the second mutation may not be identified by the state's panel. For states that perform two IRT tests, sweat testing is also the definitive confirmatory test. Sweat testing can be reliably performed after one week of life. Currently, a sweat chloride level of 60 mmol/L is diagnostic of CF; a value ranging from 30 mmol/L to 59 mmol/L is a borderline result that requires a repeat test and/or DNA analysis (if not previously performed). About 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 that 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

This enzyme deficiency prevents the recycling of the vitamin biotin. It can result in seizures, infections, hearing loss, 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 due to 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 livebirths. 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. Since newborns with the salt wasting form can have life threatening salt wasting crises, rapid identification of the 21-hydroxylase form through NBS 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

This disorder 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 due to 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, about 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 GALT enzyme (galactose-1 phosphate uridylyltransferase) 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 about 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 infants are not identified as hearing impaired until 2–3 years of age. The number of infants born with significant permanent hearing loss is estimated at 1–3/1,000, with an estimated 3/1,000 with moderate hearing loss.¹⁸ Newborn hearing screening is typically performed by evoked otoacoustic emissions or by the auditory brainstem 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 baby’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 brainstem response measures, three surface electrodes are placed on the forehead, nape, and mastoid to detect waveforms recorded from stimuli given at 35 decibels (dB). The waveforms generated are compared to 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 30–40dB HL (decibels Hearing Level) or greater across the frequencies of 500–4000 hertz, 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 (SCID) is a primary immune deficiency syndrome with a severe defect in both the T and B lymphocytes. It is the first newborn screening disorder that is DNA based for identification. It causes an increased susceptibility to a variety of infections as well as failure to thrive. Children with untreated SCID have a life expectancy of about two years. Treatment consists mainly of early bone marrow transplant. Currently about eight states screen for SCID; 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 livebirths.²⁰

Critical Congenital heart disease

Congenital heart disease affects about 8:1,000 newborns and accounts for 24% of all infant deaths due to congenital birth defects.²¹ The subgroup of critical congenital heart disease (CCHD) 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 SACHDNC voted to add CCHD to the core panel, recommending the use of pulse oximetry to identify CCHD in newborns. The non invasive 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 HRSA should guide screening standards and infrastructure for this program. As of February, 2012, only New Jersey was screening for CCHD.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 impact 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 NBS expands and adopts new technologies.^{22,23}

The original criteria for adding a condition to NBS panels suggested that an immediate, lifesaving 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 NBS 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 utility. 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 NBS 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 a 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 NBS, 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 associate 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 NBS is completed. Others, such as Michigan, have undertaken a parental engagement process which has garnered support for research on residual bloodspots 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 NBS enter their reproductive years. Newborns who were diagnosed with PKU 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 PKU 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 neurological consequences of elevated maternal phenylalanine levels. Identifying women with PKU 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

Since 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. While 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 of Newborn screening, which recommends educating parents about newborn screening prior to birth at any time during the prenatal period.⁴ It lists resources for both providers and patients to make information about NBS easily accessible. This recommendation is based on prior evidence from focus groups and surveys that women and their families wish to understand NBS prior to delivery.^{3, 30} Given that health information regarding specific NBS diseases is difficult to understand, simple brochures explaining the process are essential.

Conclusion: Current and Future Challenges

Public health departments must continue to maintain NBS 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 prior to 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 due to issues of illness or home birth, or due to 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, in order 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 prior to delivery

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