Newborn Screening: Current Status

Much progress has been made, but the infrastructure needed for comprehensive newborn screening is not yet available.

by Pamela H. Arn

ABSTRACT: Newborn screening, which represents one of the major advances in child health of the past century, has been carried out in all fifty U.S. states since the 1970s. Newborn screening programs are state-run, and decisions are left to the individual states regarding the conditions to be screened for, the mechanism for confirmatory testing, follow-up care, and financing of the programs. Laboratory advances in tandem mass spectrometry make it possible to screen newborns for many rare inborn errors of metabolism. This raises many policy issues including screening’s cost-effectiveness, ethics, quality, and oversight. [Health Affairs 26, no. 2 (2007): 559–566; 10.1377/hlthaff.26.2.559]

An estimated 4.1 million infants are screened annually in the United States for genetic metabolic disorders. U.S. newborn screening programs began in the early 1960s with phenylketonuria (PKU), a disorder of protein metabolism that causes mental retardation when untreated. Babies with PKU appear normal at birth, but the severe developmental disabilities associated with the condition can be avoided with early dietary treatment. Screening for PKU was followed by screening for congenital hypothyroidism in the early 1970s, based on the success of PKU screening and treatment and on the ability to prevent severe disability in another group of children.

Evolving screening capabilities. Each state is now responsible for its own newborn screening program. State legislatures play a key role in the newborn screening system, since they are (at a minimum) responsible for appropriating funds or authorizing fees to make the screening program possible. In all cases, the primary responsibility for newborn screening resides in the public health system, which faces many challenges as newborn screening capabilities evolve.

Until the past few years, there was little controversy regarding state-run newborn screening programs. All fifty states screened for PKU and hypothyroidism; some states included galactosemia (a disorder of lactose metabolism that can cause liver failure and death if untreated) and hemoglobinopathies (such as sickle cell anemia), and a few screened for other rare disorders. Historically, for each dis-

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order screened, a separate test was required, each with its associated costs and the need for a portion of the blood specimen, thus limiting the number of tests that could be done.2

In the early 1980s, with the advent of the technique of tandem mass spectrometry (MS/MS), it became possible to screen for a sizable number of conditions on a single blood specimen in a timely fashion. In 1990, David Millington proposed using MS/MS analysis of dried blood spots for newborn screening.3 With this technique, a profile of as many as fifteen different markers and ratios of metabolites (known as an acylcarnitine profile) can be determined using a very small amount of blood. This allows a single procedure to screen for thirty or more inherited disorders.4 By the mid-1990s it was possible to screen for amino acid, organic acid, and fatty acid disorders in the same procedure. The increase in the number of inherited metabolic disorders detectable in the newborn period extended the possibilities of early, generally presymptomatic, diagnosis and treatment. This minimized morbidity and mortality for many affected children but also raised questions of cost-effectiveness, treatment efficacy, ethics, and lack of data regarding the natural history of some of the disorders.5 As a result of funding problems and lack of data regarding outcomes, not every state incorporated the new technologies into their screening programs.

Growing disparities in screening programs. Private laboratories began offering newborn screening tests either by contracting with individual hospitals or states, or both, or by offering tests directly to the community as public awareness of these conditions grew. All of these factors contributed to growing disparities in screening programs across states. Pressure to adopt expanded screening has come from physicians, patient advocacy groups, and legal actions brought by the parents of children with genetic disorders that were not detected by screening. By as early as 2003, almost half of the states had implemented MS/MS screening, but the number and types of conditions for which they were screening still varied.

Modern Developments In Newborn Screening

The criteria of James M.G. Wilson and Gunnar Jungner were proposed in the 1960s to assess the validity of screening for a given condition. These criteria were as follows: (1) The condition being screened for should be an important health problem; (2) the natural history of the condition should be well understood; (3) there should be a detectable early stage; (4) treatment at an early stage should be of more benefit than at a later stage; (5) a suitable test should be devised for the early stage; (6) the test should be acceptable; (7) intervals for repeating the test should be determined; (8) adequate health service provision should be made for the extra clinical workload resulting from screening; and (9) the risks, both physical and psychological, should be less than the benefits.6 The criteria were proposed before multiplex screening emerged; they consider each disease individually. Also, some aspects of the criteria (such as the importance of the health
problem) are subjective. No standard criteria are consistently used in all programs. The lack of uniformity in newborn screening programs and the complexity of assessment led the American Academy of Pediatrics (AAP) Newborn Screening Task Force to recommend “that the Health Resources and Services Administration (HRSA) should engage in a national process involving government, professionals, and consumers to...assist in the development and implementation of nationally recognized newborn screening system standards and policies.” HRSA’s Maternal and Child Health Bureau (MCHB) also commissioned the American College of Medical Genetics (ACMG) to outline a process to standardize outcomes and guidelines for state newborn screening programs and to define responsibilities for collecting and evaluating outcome data, including a recommended uniform panel of conditions to include in state newborn screening programs.

The ACMG formed a group (the Newborn Screening Expert Group) that included subspecialists; primary care physicians; consumers; and experts in law, ethics, and public health to make recommendations regarding newborn screening. The methods used and details of the deliberations were published in a special report; the diseases that the ACMG recommended for screening are listed in Exhibit 1. These twenty-nine conditions were recommended because the group concluded that a screening test and a treatment were available for each, and adequate information about the natural history was known. Many of the diseases chosen are rare individually, but when considered together, they make up a major cause of pediatric morbidity and mortality. Some of the diseases are unfamiliar even to pediatricians, thus complicating diagnosis without screening. The expert group also identified twenty-five additional conditions that may be considered for screening. Metabolites of these conditions may be detected on newborn screening, and the diseases associated with these metabolites may be reported in some programs. Current screening panels for all states can be found at the national newborn screening and genetics resource center.

Value Of Screening Programs

Genetic diseases involving metabolism, also known as inborn errors of metabolism, generally fall into two broad categories: diseases of intoxication and diseases of fatty acid oxidation. In disorders of intoxication, there is a progressive accumulation of metabolites that are toxic to a newborn because a key enzyme in a metabolic pathway is lacking. Diseases 1–15 and 27 (Exhibit 1) fall into this category. Treatment is available for these disorders, and early intervention prior to the development of symptoms generally results in an improved outcome.

Disorders of fatty acid oxidation (diseases 16–20, Exhibit 1) include medium-chain acyl-CoA dehydrogenase (MCAD) deficiency. This disorder was an important driver of expanded screening. The most frequent clinical presentation is that of a previously normal toddler with hypoglycemia, coma, and seizures after a short illness. MCAD is one of the most common inborn errors, with incidence estimates...
of 1 per 10,000 births in some populations. Approximately 20 percent of undiagnosed children will die during the initial episode, and 20 percent more will suffer irreversible neurological damage related to coma and hypoglycemia.\textsuperscript{11} In a report from Australia, 21 percent of unscreened children with MCAD died, while only one child who had been screened died. Once parents are informed of a child’s diagnosis, the risk of coma, seizures, and death can be essentially eliminated if the child is not allowed to fast.\textsuperscript{12}

**Current Program Issues**

\textbf{Scientific issues.} Because of the success of treating MCAD and other diseases, it has been hoped that early intervention in other inborn errors will also result in improved outcomes. The aim of newborn screening is, after all, to improve outcomes by early detection of disease. Data are lacking, however, in the areas of the cost-effectiveness of screening, treatment efficacy, and natural history for some conditions.

It has been pointed out that evidence in inborn errors of metabolism in general is either not available or difficult to locate.\textsuperscript{13} This does not mean that there can be no evidence-based policy in newborn screening, however. Although randomized controlled trials (RCTs) might not be feasible in the case of rare conditions, observation and expert opinion contribute to evidence and are valuable for informing screening decisions. Policymakers often must make decisions when evidence is in dispute or not available. In these cases, they must be explicit about the elements of the decision-making process and the evidence base for policy.\textsuperscript{14}

Efforts are under way to gather information after screening is implemented through the National Coordinating Center for the Genetics and Newborn Screen-
ing Regional Collaborative Groups. This is the result of a partnership among the Genetic Services Branch, HRSA, the MCHB, and the ACMG. Participation by states and regions is voluntary.\textsuperscript{15}

**Funding issues.** Only a few studies have attempted to do a comprehensive cost-utility analysis of newborn screening. MCAD has been the most commonly analyzed disorder. It has been the most commonly cited for cost-effectiveness, since the treatment for MCAD is quite effective and has been shown to prevent severe neurologic sequelae. Almost all of the additional costs of screening for MCAD are offset by avoided sequelae in some models. A study that looked at a cost-utility analysis of MS/MS screening in a more comprehensive disease panel of diseases concluded, “Newborn screening seems to be one of the rare health care interventions that is beneficial to patients, and, with some assumptions, cost saving.”\textsuperscript{16} Long-term evidence is lacking in many areas, however. False positive results consume resources that might be difficult to quantify.

Each state newborn screening program is unique in its administrative and financing structure. The majority of states collect fees as the primary source of program funding. These fees may be collected from hospitals, patients, or third-party payers. To a lesser extent, Medicaid, Title V Maternal and Child Health Services Block Grants, and state general revenue funding are used. Most newborn screening funds, however, do not come from federal or state general revenues (Exhibit 2).

Nationwide data on funding sources and uses for services related to newborn screening are not collected routinely. A 2003 report by the U.S. Government Accountability Office (GAO) noted that in state fiscal year 2001, more than $120 million was spent on screening programs. This averaged approximately $30 per infant screened, and most of the fees collected are used to support laboratory analysis. Fewer than half of the states provide financing for genetic or nutritional counseling and long-term follow-up.\textsuperscript{17}

**Health system needs.** Care of children with metabolic diseases is complex, involving primary care physicians, metabolic specialists, genetic counselors, and

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**EXHIBIT 2**

**Sources Of Funding For Newborn Screening, 2003**

<table>
<thead>
<tr>
<th>Source</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fees</td>
<td>60%</td>
</tr>
<tr>
<td>Other funds</td>
<td>5%</td>
</tr>
<tr>
<td>Other state funding</td>
<td>20%</td>
</tr>
<tr>
<td>Medicaid</td>
<td>10%</td>
</tr>
<tr>
<td>Title V MCH Services Block Grant</td>
<td>5%</td>
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</tbody>
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**NOTE:** MCH is Maternal and Child Health.
metabolic nutritionists. Even when the initial screening is successfully funded and completed, confirmation of diagnosis and long-term management are challenging. Actual laboratories are often not part of the state system, thus requiring insurance approvals to access necessary testing in a timely fashion. Few states have an integrated system of care that allows screening, confirmation, and follow-up to occur seamlessly. Newborn screening involves education of physicians and parents, definitive diagnosis, long-term management, and quality evaluation. If all of these components of a program are not in place, cost-savings benefits might not be fully realized, and optimal patient outcomes might not be achieved.

Quality and training needs. Considerable need exists for education and training throughout the health care system, since very few physicians have been trained to manage children with inborn errors of metabolism. There are also very few people trained to oversee biochemical genetics testing laboratories. Since the 1980s there has been a progressive decline in the number of biochemical specialty laboratories, and clinical biochemical specialists are in short supply. The biochemical specialty laboratories that traditionally provided diagnostic services for these rare diseases had limited capacity and limited services, which made it difficult for them to compete financially. Few labs in the country, therefore, are equipped to quickly and accurately provide definitive diagnostics for a positive newborn screen. Also, enrollment of young physicians and people with doctorates in biochemical genetics programs declined in the 1990s because of funding problems and greater interest in molecular genetics.

Lack of quality assurance systems. Managing diagnostic and confirmatory testing has pitfalls, since the abnormal analyte increases found in MS/MS screening are not always diagnostic of a single disorder; therefore, additional molecular and biochemical testing often must be performed. Comprehensive quality assurance systems are not yet in place to define targets and perform interlaboratory comparisons, although some programs do address technical aspects of the testing. Most of these quality assurance programs are voluntary. To address this issue, Pierro Rinaldo and colleagues proposed laboratory standards that include targets reflecting analytical and postanalytical performance markers, such as detection rate, positive predictive value, and false positive rate. The proposed false positive rate is <0.3 percent, with a positive predictive value of >20 percent.

False positive results and their effect on families have been a concern raised by physicians and policymakers. Beth Tarini and colleagues published estimates of the theoretical number of false positive results in expanded screening programs. Although these estimates call attention to the potential negative impact on the public and on the newborn screening system, actual data need to be collected and reported. At least one study has directly shown that false positive screening results increase parental stress and may increase risk for abnormal parent-child interactions. The increased use of a second tier of testing within the newborn screening laboratory might help lower the false positive rate but also must not de-
lay diagnosis in an affected child. This has become possible because of progress in human genetics, since now the most common gene mutations are known for many diseases (cystic fibrosis and MCAD, for example). Mutation analysis can be performed using the blood from the newborn screening card, thus increasing specificity. However, families and physicians might still be left to cope with results that have uncertain clinical significance.

**Future Directions**

Although progress has been made in the adoption of expanded screening over the past few years, more needs to be done to achieve a consistent, equitable, and high-quality national newborn screening program. Up to 23 percent of U.S. newborns are still not screened for MCAD, a disease that is diagnosed by a test that most models generally agree is clinically sound and cost-effective. At the same time, infants are being screened for conditions that are rarer and less treatable than MCAD.

As advances in biochemical and molecular genetics occur, it becomes technically possible to add more diseases to the list that can be considered for testing. Already, there is discussion about adding even more diseases in some states. Policymakers will continue to struggle with these issues and that there is need for continuing national discussion. To assist in improving screening and outcome measures, it has been suggested that the new technology should be introduced within a research paradigm, to facilitate data collection. This is difficult, however, given the existence of fifty independent state programs. Regionalization of screening and the laboratories that are able to diagnose, confirm, and monitor metabolite levels would facilitate quality assurance and improve the consistency of data collection. The needed infrastructure is not available, and education of the public and the medical community is lacking. Implementation of newborn screening in a way that will eventually lead to a true evidence-based approach will require collaboration, education, adequate funding for research, and an infrastructure that provides a larger role for a central body (likely the federal government). Until data are collected and available, an evidence-based approach is not possible. Policymakers must try to balance the costs and the benefits, taking into account the weight that the medical community and the public place on screening.

**NOTES**


15. For more information, go to the National Coordinating Center's home page, http://www.nccrcg.org.


