

## CDC Grand Rounds: Newborn Screening and Improved Outcomes

Newborn screening is the practice of testing every newborn for certain harmful or potentially fatal conditions, such as hearing loss and certain genetic, endocrine, and metabolic disorders that typically are not otherwise apparent at birth. Newborn screening in the United States began in the 1960s. Universal newborn screening has become a well-established, state-based, public health system involving education, screening, diagnostic follow-up, treatment and management, and system monitoring and evaluation (1). Each year, >98% of approximately 4 million newborns in the United States are screened (2,3). Through early identification, newborn screening provides an opportunity for treatment and significant reductions in morbidity and mortality (2,3).

### Uniformity of Newborn Screening

In 2006, The American College of Medical Genetics (ACMG), under the aegis of the Health Resources and Services Administration (HRSA), convened a group of experts to address the substantial variation in the number of disorders screened for in each state. The experts evaluated scientific and medical information related to screened conditions and recommended a uniform screening panel of 29 core (or primary) conditions to be included in state newborn screening panels: 20 inborn errors of metabolism, three hemoglobinopathies, and six other conditions (4). This panel was endorsed by the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) and designated by the Secretary of the U.S. Department of Health and Human Services as a national standard for newborn screening programs (4). Its adoption has led to increased uniformity of screening in the United States and its territories (Figure 1) (2,3). Additional conditions for screening continue to be identified and nominated for inclusion in the panel.

### Expansion of Newborn Screening

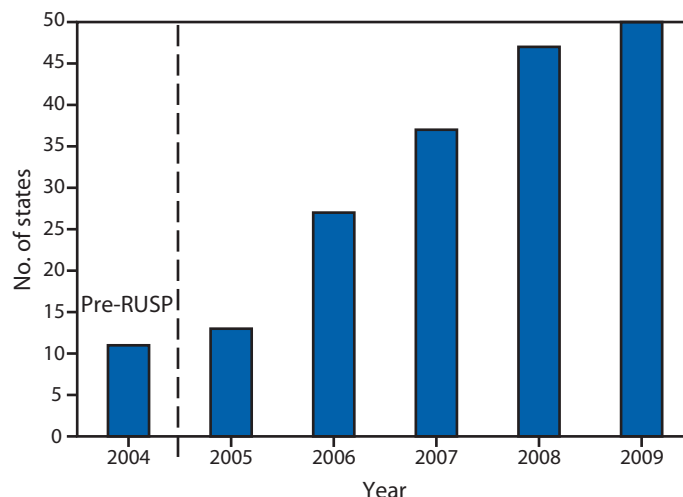
ACHDNC reviews nominations of conditions to be included in the uniform panel. The committee encourages nomination by persons and organizations with expertise on the condition being nominated. The nomination process is transparent, allows for public commentary, and follows a systematic protocol for evidence-based review (5). Since adoption of the core panel of 29 conditions, nine additional conditions have been submitted and reviewed. ACHDNC recommendations to include two of the conditions, severe combined immunodeficiency and critical congenital heart disease, into the uniform newborn screening panel were approved by the Secretary in 2010 and

2011, respectively. Six of the conditions submitted for inclusion have been forwarded for an external review, and four have been referred back to nominators for additional studies.

### Public Health Burden

Of the 4 million infants who are screened each year, approximately 12,500 are diagnosed with one of the 29 core conditions of the uniform screening panel. The five most commonly diagnosed conditions in the United States are 1) hearing loss, 2) primary congenital hypothyroidism, 3) cystic fibrosis, 4) sickle cell disease, and 5) medium-chain acyl-CoA dehydrogenase deficiency (Table) (3,6). Newborn screening can help prevent death or disability, if treatment follows (1,3). Each year, for example, one in 2,000 newborns is diagnosed with congenital hypothyroidism. Screening followed by thyroid hormone treatment can prevent intellectual disability (intelligence quotient [IQ] score <70) (7,8). Congenital hearing loss occurs in one to three newborns per 1,000 live births. Each year, newborn hearing screening identifies hearing loss in >5,000 infants. Without screening, these children might have delayed language acquisition, low educational attainment, increased behavior problems, decreased psychosocial well-being, and poor adaptive skills (9). Untreated phenylketonuria can result in severe cognitive impairment. Prompt initiation of treatment following newborn screening is essential for optimal development and prevention of disability (10).

**FIGURE 1. Number of states screening for the core bloodspot conditions in the Recommended Uniform Screening Panel (RUSP) — United States, 2004–2009**



Source: Data reported from National Newborn Screening and Genetics Resource Center. Available at <http://genes-r-us.uthscsa.edu>.

**TABLE. Estimated number of cases among U.S. children identified in 2006 with disorders listed in the Recommended Uniform Screening Panel,\* based on incidence of these disorders in four state newborn screening programs during 2001–2006,† and number diagnosed with hearing loss in 2009‡**

Disorder	Estimated no. of cases
Hearing loss	5,073
Primary congenital hypothyroidism (excluding secondary, transient, or other)	2,156
Cystic fibrosis (including nonclassical)	1,248
Hemoglobin SS (sickle cell anemia)	1,128
Hemoglobin SC (sickle C disease)	484
Medium-chain acyl-CoA dehydrogenase deficiency	239
Classical galactosemia (GALT) plus variant (excluding GALK and GALE)	224
Phenylketonuria (PKU), including clinically significant hyperphenylalaninemia variants	215
Congenital adrenal hyperplasia (excluding non 21-hydroxylase deficiency)	202
Hemoglobin S/β thalassemia	163
3-Methylcrotonyl-CoA carboxylase deficiency	100
Carnitine uptake defect	85
Very long-chain acyl-CoA dehydrogenase deficiency	69
Biotinidase deficiency (including partial)	62
Methylmalonic acidemia (mutase deficiency)	50
Glutaric acidemia type I	38
Isovaleric acidemia	32
Maple syrup urine disease	26
Citrullinemia type I	24
Propionic acidemia	15
Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency	13
Methylmalonic acidemia CbIA,B	12
Homocystinuria	11
Argininosuccinic acidemia	7
Beta-ketothiolase deficiency	7
Hydroxymethylglutaric aciduria	3
Multiple carboxylase deficiency	3
Trifunctional protein deficiency	2
<b>Total</b>	<b>11, 691</b>

\* One of the 29 disorders listed in the screening panel (tyrosinemia type 1), and two recently approved additions (severe combined immunodeficiency and critical congenital heart disease) are not included in this table. Listing available at [http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritable\\_disorders/recommendedpanel/index.html](http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritable_disorders/recommendedpanel/index.html).

† The four states were California, Massachusetts, North Carolina, and Wisconsin. Source: CDC. Impact of expanded newborn screening—United States, 2006. *MMWR* 2008;57:1012–5.

‡ Estimated number of U.S. cases of hearing loss was obtained from CDC Early Hearing Detection and Intervention Program annual data. Available at <http://www.cdc.gov/ncbddd/hearingloss/ehdi-data2009.html>.

Assessing the health benefits and return on investment of newborn screening has its challenges, given the diversity of conditions and their varying outcomes. Overall, screening and treating disabling conditions can reduce health-care costs. The conditions on the uniform newborn screening panel, with the exception of hearing loss and critical congenital heart disease, all are detected by dried blood spot screening. The cost of the U.S. newborn blood spot screening system was assessed by the U.S. Government Accountability Office in 2003 at \$120 million per year, or \$30 per infant (11). For congenital hypothyroidism

alone, the most recent estimate of the annual cost of testing is \$5 per infant, or \$20 million for the entire country (12). The potential health benefit of testing 4 million infants for congenital hypothyroidism is the prevention of 160 cases of intellectual disability and, among 1,010 infants in whom milder impairments (i.e., IQ scores lower than expected for the population) were prevented, a total gain of nearly 15,000 IQ points (8).

**Laboratory expertise for newborn screening tests.** Most newborn screening is conducted by state health laboratories, which follow prescribed procedures to ensure high-quality screening and communicate results and information with other segments of the newborn screening system, such as hospitals and health-care practitioners. They also play an important role in conducting translational research by identifying and designing new screening tests and focusing on quality improvement of current screening tests. Their challenges include an environment of restricted state budgets, an increase in the number of new conditions that need to be detected, and the need to stay current with evolving technologies and automate processes to reduce cost.

CDC works with state and regional newborn screening laboratories to develop and improve the quality of screening tests. CDC administers the Newborn Screening Quality Assurance Program, which includes all U.S. laboratories involved in newborn screening and >450 international laboratories. This is the only program that addresses quality issues of dried blood spot measurements for all conditions for which newborn screening is available in the United States. The program provides proficiency testing, training, support, technical assistance, and consultation to participating laboratories.

**Long-term follow-up.** The goal of long-term follow-up is to improve the quality of care for children with diagnosed disorders so that they receive timely, appropriate care (13). Strategies for comprehensive long-term follow-up include coordination of multidisciplinary care through a child's medical home,\* monitoring physical and psychosocial outcomes, improving family and provider access to information, establishing evidence-based best practices, and improving quality and timeliness of follow-up, diagnosis, and treatment and management through health information technology. Long-term follow-up is used to assess the needs of patients and families regarding disease management, treatment, and age-appropriate preventive care. Long-term follow-up can provide invaluable data to guide treatment through the development of care guidelines and clinical decision support. In the United States, however,

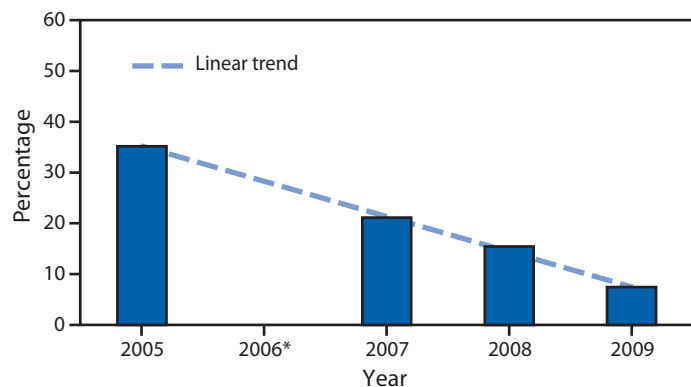
\* Defined as a partnership between a child, a child's family, and the pediatric-care team who oversees the child's health and well-being and works to ensure that all of the medical and nonmedical needs of the patient are met. The medical home is a model of delivering care that is accessible, continuous, and comprehensive.

newborn screening resources often are focused on diagnosis and short-term follow-up, and long-term follow-up among state programs varies considerably. A 2005 survey of state newborn screening programs found that only 56% routinely conduct systematic long-term follow-up (14).

**Data systems and tracking for follow-up and management of disorders.** Improvement of data quality in overall tracking and surveillance systems is needed to track the clinical outcomes of affected children more effectively and to refine protocols for short-term and long-term follow-up of children with conditions identified through newborn screening. For example, newborn screening for hearing loss increased from 46.5% in 1999 to 96.9% in 2008, but data on follow-up testing are lacking. In 2009, nearly 45% of infants who did not pass screens lacked documentation of a follow-up assessment (6). The Indiana newborn hearing screening program is exemplary for its web-based tracking and surveillance system, which includes follow-up reminders and quality improvement activities. Indiana has shown a dramatic decrease in the percentage of infants who are lost to follow-up and documentation, from 35% in 2005 to 7% in 2009 (6) (Figure 2).

Data transmission between clinical care and public health systems is needed to improve follow-up and management. CDC, HRSA, the National Institutes of Health, and the National Library of Medicine are working with state programs and clinicians to describe common variables and standardize data collection procedures to enable different segments of the newborn screening system to share information. Another challenge is that states might differ in the case definitions they use for newborn screening disorders. To create multistate datasets for newborn screening disorders, federal agencies are collaborating with clinicians to develop standardized case definitions for use in state and national newborn screening data collection.

**FIGURE 2. Infants lost to follow-up and documentation after hearing screening — Indiana, 2005–2009**



\* Data for 2006 were incomplete because of changes in the program.

**Building partnerships.** The need for improvements in long-term follow-up provides opportunities for partnerships at the national, state, and local levels. National partnerships provide a forum for health-care providers, public health professionals, and families to collaborate on newborn screening issues such as data collection, education, laboratory services, and clinical care. At the state and local level, partnerships should be established among state newborn screening programs, Title V programs, professional societies, and health-care providers. Resources to support these partnerships include the HRSA-funded Regional Genetic and Newborn Screening Services Collaboratives, the National Institutes of Health-funded Newborn Screening Translational Research Network, the Genetic Alliance, the National Newborn Screening and Genetics Resource Center, and the National Center on Hearing Assessment and Management. Initiatives designed to improve quality and develop the evidence base for treatment include the Newborn Screening ACTION Quality Improvement Innovation Network and the Newborn Screening Education in Quality Improvement for Pediatric Practice course, which include decision support tools for the clinical practice and education of primary-care providers, assisting them in identifying and closing gaps in care. Learning collaboratives, such as the National Initiative for Children's Healthcare Quality/Maternal Child Health Bureau project, have been developed to help state programs improve hearing screening services and enhance data collection and registries.

## Summary

Although newborn screening capabilities have improved and expanded significantly in the past decade, several critical gaps and challenges remain. Clinical challenges include a shortage of experts trained to diagnose and manage conditions detected by newborn screening. Laboratory gaps and opportunities center on detection of multiple conditions using a single test, expansion of automation to reduce testing costs, and extension of new molecular methods to all disorders. General challenges include a lack of public education and understanding about the value of newborn screening that could be improved by deeper engagement of consumers in newborn screening policy and program development. Advocacy organizations can assist with raising awareness of newborn screening and can provide disease-specific education to the public. In 2009, HRSA awarded a cooperative agreement to Genetic Alliance, a consumer advocacy group, to develop a newborn screening clearinghouse. The clearinghouse was launched in September 2011 as an online resource<sup>†</sup> that provides information on newborn

<sup>†</sup> Available at <http://www.babysfirsttest.org>.

screening, the conditions the tests identify, and screening information for all 50 states, the District of Columbia, Puerto Rico, and U.S. territories. This is a national level resource providing comprehensive education for families. Continued collaboration among partners provides an excellent opportunity to enhance laboratory and data systems through quality assurance, surveillance, tracking, and research to improve screening techniques, better guide follow-up of affected children, and optimize outcomes.

Given all these challenges and opportunities, screening itself clearly is not enough. It is critical to avoid complacency in assuming that every newborn who is screened will receive optimal service and care. Short-term follow-up and management of children with disorders and long-term follow-up activities within the entire newborn screening system are central to realizing the promise of newborn screening.

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