Newborn screening—the unique role of unique evidence

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In this issue of *Genetics in Medicine*, there are several articles on newborn screening including two that describe how the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children proposes to deal with both the unique challenge of evaluating new conditions nominated for population-based newborn screening[1] and the adaptation of the standard evidence review process to screening for rare diseases.[2] Newborn screening is a public health program that provides early identification of genetic, metabolic, hormonal, and functional disorders among infants for the purpose of follow-up care and treatment. Without treatment, the screened for disorders can result in devastating health consequences and in some cases, death. Recent figures estimate that the national newborn screening program identifies >5000 children per year in the United States with treatable metabolic, hematologic, or hormonal disorders, and another 12,000 with hearing deficits who require intervention.[3,4]

Newborn screening began in the 1960s as a direct result of important discoveries in the laboratory of Dr. Robert Guthrie who developed a simple blood test to identify newborns affected with a rare but serious and treatable metabolic disorder, phenylketonuria.[5] Over the last several decades, with major advances in the identification and treatment of rare diseases, new technologies to facilitate universal screening, and broad-based advocacy in every state, the newborn screening program has expanded. In 2005, the US Health Resources and Services Administration commissioned the American College of Medical Genetics (ACMG) to develop national recommendations for newborn screening. The ACMG report recommended mandatory newborn screening for a core panel of 29 conditions[6]; and today, newborns in every state in the United States and the District of Columbia are screened for at least 26 of those recommended disorders.[7] The ACMG report was enthusiastically endorsed by the Secretary's Advisory Committee as well as the American Academy of Pediatrics, the March of Dimes, and other organizations.

In recent years, several articles have criticized the methodology used to determine the disorders recommended for screening in the core panel,[8,9] primarily arguing that the original process did not conform to contemporary standards of evidence-based decision making for public health screening programs. The process for developing the recommended panel of tests included the work of a multidisciplinary committee appointed by the ACMG to review the extant literature related to each disorder and solicitation of opinion from a broad expert group. The ACMG criteria for inclusion of a disorder in the recommended panel were the ability to identify the disorder before symptom development through a sensitive and specific test performed within the first 24 to 48 hours after birth and demonstrated benefit of early detection, timely intervention, and efficacious treatment of the condition.[1] Certainly, reasonable people may disagree on the definition of "demonstrated benefit" and "efficacious treatment," but the ACMG group of experts took those concerns quite seriously in evaluating the available evidence. The group had to deal with the difficult realization that for many of the recommended conditions, there are scant data from large-scale population screening studies and few randomized clinical trials or well-designed longitudinal cohort studies that might offer an optimal level evidence of efficacy.

The Secretary's Advisory Committee, chartered in 2003, has the responsibility for making recommendations to the Secretary of Health and Human Services regarding those serious health conditions for which newborns should be tested. From the outset, the committee recognized that few if any prior review groups were experienced in evaluations of new screening methodologies for rare disorders for which there is a paucity of information on the clinical utility of screening, the range of phenotypic expression of detected genotypes, the potential effectiveness of medical treatments or other management options, and the impact of false-positive tests. The committee reviewed the approach of several review groups including the US Preventive Services Task Force and concluded that the threshold for evidence-based public health practice for screening for rare diseases is intrinsically different from evidence-based clinical practice, and from the approach that is ideally suited for determining appropriateness of population-based screening tests for more common chronic conditions such as cancer, cardiovascular disease, or diabetes.[10]

To assist in the evaluation of new conditions nominated for inclusion in population-based newborn screening, the Secretary's Advisory Committee created an Evidence Work Group to review all of the published evidence as well as to obtain data from experts on unpublished information related to each disorder. The Work Group presents a synthesis of the evidence for review by the committee. The committee has created a set of probing questions to assist in the review of the information from the Work Group that ultimately results in a recommendation about each nominated disorder. Although several nominated conditions have been through this process, to date, no new disorders have been recommended for inclusion in the core panel.

Recent experience with the new US Preventive Services Task Force recommendations for mammography[11] reminds us that even when there is high level evidence from multiple studies and sufficient data, generally there is criticism when expert groups make recommendations about population-based screening. Members of the public often voice concern that lack of screening can result in the death of a patient from a potentially preventable or treatable disorder, and on the other hand, some may argue that the consequences of false-positive results or the costs of the program do not justify universal screening. These concerns will affect public perception of the validity and desir-

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ability of any recommendations. That is the reason that recommendations for public health screening programs should be made by a consistent and rigorous process that includes careful assessment of the evidence, elimination of conflicts of interest, and transparency with significant public input throughout. In addition, each such recommendation should be accompanied by a robust risk communication and education program for health professionals and the public to clarify the distinction between individual clinical indications for testing and public health screening standards.

The process described by the Secretary's Advisory Committee and its Evidence Review Group to adapt the standard population-based evidence review approach to screening for rare disorders in newborns is a credible and appropriate response to this challenging task. We applaud this careful and thoughtful approach and look forward to the successful application of this process to provide national recommendations for additional disorders to be added to the newborn screening core panel. Most importantly, we believe that this approach serves the interests of the public, the affected children, and their families.

REFERENCES

1. Calonge N, Green NS, Rinaldo P, et al. Committee report: method for evaluating conditions nominated for population-based screening of newborns and children. *Genet Med* 2010;3:153–159.
2. Perrin JM, Knapp AA, Browning M, et al. An evidence development process for newborn screening. *Genet Med* 2010;3:131–134.
3. The Centers for Disease Control and Prevention, Division of Laboratory Sciences. Quality assurance and proficiency testing for newborn screening. Available at: http://www.cdc.gov/nceh/dls/newborn.htm. Accessed December 17, 2009.
4. National Center for Hearing Assessment & Management, Early Hearing Detection and Intervention/Universal Newborn Hearing Screening. Available at: www.infanthearing.org/resources.html. Accessed December 17, 2009.
5. Howse JL, Weiss M, Green NS. Critical role of the March of Dimes in the expansion of newborn screening. *Ment Retard Dev Disabil Res Rev* 2006; 12:280–287.
6. Watson MS, Lloyd-Puryear MA, Mann MY, Rinaldo P, Howell RR, editors. Newborn screening: toward a uniform screening panel and system. Main report. *Genet Med* 2006;8(suppl):1S–11S.
7. National Newborn Screening and Genetics Resource Center. National newborn screening status report. Available at: http://genes-rus.uthscsa.edu/nbsdisorders. Accessed November 20, 2007.
8. Botkin JR, Clayton EW, Fost NC, et al. Newborn screening technology: proceed with caution. *Pediatrics* 2006;117:1793–1799.
9. Moyer VA, Calonge N, Teutsch SM, Botkin JR; United States Preventive Services Task Force. Expanding newborn screening: process, policy, and priorities. *Hastings Cent Rep* 2008;38:32–39.
10. Guirguis-Blake J, Calonge N, Miller T, Siu A, Teutsch S, Whitlock E; U.S. Preventive Services Task Force. Current processes of the US Preventive Services Task Force: refining evidence-based recommendation development. *Ann Intern Med* 2007;147:117–122.
11. US Preventive Services Task Force. Screening for breast cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2009;151:716–726.