Assisting States in Assessing Newborn Screening Options

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Reports in the popular media have called attention to the inconsistencies among US programs designed for screening newborns for inherited disorders that can be fatal or disabling if not identified soon after birth. In the absence of federal guidelines, each of the 50 states has taken on newborn screening as a public health responsibility, and this has resulted in variations in the number of state-mandated tests for newborns from three to 11.[1] Concerns about missed opportunities to screen children for serious conditions before they become sick have led parent advocacy groups to call for more uniform implementation of screening tests. The emergence of new technologies that make screening for more conditions possible has contributed to calls for states either to incorporate new technologies and tests in state-based laboratory testing programs, or to allow hospitals to use private laboratory screening that includes a broader range of tests than those provided by state-based programs.

Massachusetts was one of the first states to engage in a public debate about expanding newborn screening. The article in this issue by Atkinson et al. describes the public process by which the Massachusetts Department of Public Health, during 1997 and 1998, considered which tests to recommend adding to the newborn screening panel. That article provides a model for consideration by other states.[2] It also makes clear that the impetus for this process was the challenge by parent advocacy groups, collaborating with for-profit screening laboratories, that Massachusetts either include expanded newborn screening using the new technology of tandem mass spectrometry (MS/MS) in the state-based screening program or allow the private sector to provide the service instead.

In response, the Department of Public Health selected a group of medical and technical experts to form the Massachusetts Newborn Screening Advisory Committee, which also included a lay member to represent the public. The

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Editor's note: In this commentary, the term *MS/MS* is used in place of *tandem MS*, which was used in the article, "A Public Health Response to Emerging Technology: Expansion of the Massachusetts Screening Program" (page 122).

Committee was mandated to hold a series of public meetings to ensure broad input into its deliberations and recommendations. Only half of the states have an advisory committee for newborn screening with consumer representation.[3]

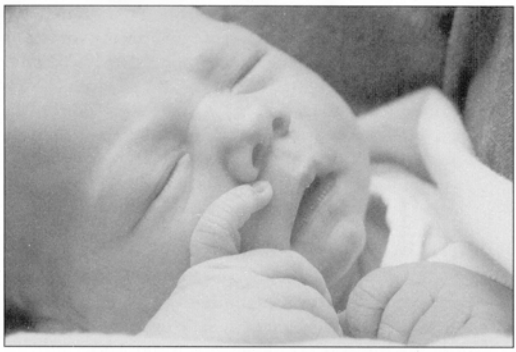
The Massachusetts Advisory Committee addressed the dilemma of how to assess a screening test that experts believe may benefit infants, but for which data proving such benefit are lacking. The Advisory Committee classified disorders into two groups: those for which evidence of benefit is sufficient to recommend mandatory testing and those for which evidence is not conclusive but is sufficient to recommend investigational use. The Advisory Committee found one disorder—medium chain acyl-coA dehydrogenase deficiency (MCADD)—to meet its selection criteria for mandatory testing (see below). The Advisory Committee recommended inclusion in the investigational panel of screening tests of an additional 19 conditions detectable through MS/MS, together with cystic fibrosis (CF), which is detected through other technologies. In 1997, two separate groups of experts convened by the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) recommended pilot screening for CF on an investigational basis so that more data could be amassed for use in public health genetics evaluations.[4,5] The strongest evidence of benefit from newborn screening for CF is in the prevention of chronic malnutrition, a disorder that typically has led to impaired growth.[6]

On the controversial issue of parental consent, the Massachusetts Advisory Committee steered a middle course, recommending that consent be required for some tests but not for others. Newborn screening programs across the country generally maintain that the demonstrated benefits of newborn screening justify mandating screening with exemptions only for limited reasons, chiefly religious.[3] Only Maryland and Wyoming require written parental consent for all newborn screening tests performed on blood specimens.[7,8] The Task Force on Newborn Screening sponsored by the Health Resources Services Administration (HRSA) and the American Academy of Pediatrics (AAP) in 2000 endorsed the parents' right of refusal or dissent for all newborn screening tests.[7] The approach taken by the Massachusetts Advisory Committee is consistent with the 1997 recommendation of the federal Task Force on Genetic Testing under the auspices of NIH and the Department of Energy (DOE), which recommended that consent be waived for screening tests of well-established benefit but be required for tests for which validity and utility have not yet been clearly established.[9] The informed dissent protocol in use in Massachusetts gives parents the option to decline permission for their child to be tested for nonmandatory conditions without having to provide written consent if they wish their child to be tested. These conditions include CF, for which the CDC work group recommended, "Pilot CF screening programs for newborns should be approached and promoted as research endeavors, for which participation is not mandatory and informed consent is emphasized."[5]

The criteria used to assess screening tests by the Massachusetts Advisory Committee (see Figure 1 in the article by Atkinson et al. in this issue) are not precisely defined. For example, what constitutes a sufficiently "accurate" test? Accuracy can refer to analytical validity—whether the test measures what it is supposed to measure—or clinical validity—whether the test predicts the presence or absence of a clinical condition. Which validity measure is meant? How are "positive health benefits" and "risks and burdens" quantified to determine which has the greater weight? Despite ambiguity in some of the criteria, the assessment of new tests, including those for MCADD and CF, appears to have been thorough and objective.

In Massachusetts the nine existing screening tests approved for mandatory testing do not appear to have received the same critical scrutiny from the Advisory Committee. In particular, one of the nine conditions, congenital toxoplasmosis, has not been considered by states outside the New England Newborn Screening Program to satisfy the criteria for population screening. A recent report analyzing data from the program acknowledges the "paucity of data regarding the natural course of infection."[10] Documentation by the Massachusetts Advisory Committee of how each of the screening tests proposed for inclusion in the mandatory panel satisfied the screening criteria would have been helpful. Once a test is included in a state-mandated newborn screening panel, discontinuation is difficult to justify. This asymmetry suggests caution in adding new mandated screening tests.

The Task Force on Newborn Screening sponsored by HRSA and AAP advocates a national deliberative process to inform state decision makers and to ensure more uniform access to beneficial screening tests.[7] In the United Kingdom, the Health Technology Assessment (HTA) Programme has published two systematic reviews of screening for inborn errors of metabolism.[11,12] Both reviews conclude that the evidence relating to MCADD is sufficient to justify screening newborns for this condition using MS/MS, while expressing reservations regarding other conditions detectable through MS/MS. The two reports disagree on whether all of the criteria for mandatory screening are met for



MCADD, with one of the reports pointing out that the natural history of the disorder is not well enough understood to permit quantification of the potential benefits and harms of screening.[12] In the process of deciding to mandate screening for MCADD, the Massachusetts Advisory Committee consulted the HTA report that concluded that all classical criteria for screening for MCADD are met.[11] The other HTA report,[12] which was published later, is not mentioned. A subsequent review for the CDC Human Genome Epidemiology Network (HuGE) noted that the natural history of MCADD is not well understood and called for population-based studies to demonstrate the utility of screening for MCADD.[13]

An objective process for collecting, analyzing, and interpreting data on the validity, clinical utility, and prevention effectiveness of tests and to arrive at a scientific consensus is essential. In the United States, experts agree this process will require federal funding and coordination.[7] In 1995, NIH and DOE created a Task Force on Genetic Testing to review genetic testing and to make recommendations to ensure the development of safe and effective genetic tests. The Task Force focused on tests performed on healthy or apparently healthy people to predict later onset of symptoms associated with inherited disorders. The Task Force defined genetic tests broadly to include any "analysis of human DNA, RNA, chromosomes, proteins, and certain metabolites in order to detect heritable disease-related genotypes, mutations, phenotypes, or karyotypes for clinical purposes." With the exception of congenital hypothyroidism, almost all conditions screened for in dried blood spots by newborn screening programs are inherited disorders. Hence, newborn screening tests for these conditions meet this definition of genetic tests, regardless of whether the tests involve molecular or biochemical analysis. In 1997, the Task Force on Genetic Testing recommended that the Secretary of the US Department of Health and Human Services (DHHS) convene a standing federal advisory committee to implement the recommendations in its Final Report.[9]

A new advisory committee convened in response to the report of the Task Force on Genetic Testing, the Secretary's Advisory Committee on Genetic Testing (SACGT), recently issued a broad proposal for a federal initiative to evaluate genetic tests, including tests used in population-based newborn screening.[14] The SACGT recommends that DHHS agencies collaborate with researchers and test developers to gather information on the analytic and clinical validity and clinical utility of genetic tests, and to make this information available to health care providers and the public. The SACGT further recommends that aggregation and analysis to evaluate clinical validity and utility be performed under the auspices of the CDC, which is conducting pilot studies to develop and evaluate data formats and procedures. Once these data are appropriately collected and analyzed, the SACGT suggests that an independent, objective group, such as the US Preventive Services Task Force, evaluate their relevance for policy and make appropriate recommendations. Such recommendations may eventually lead to the more uniform adoption by states of newborn screening tests of demonstrated benefit.

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