A Public Health Response to Emerging Technology: Expansion of the Massachusetts Newborn Screening Program

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SYNOPSIS

The development of a new technology, called *tandem mass spectrometry* (tandem MS), has challenged governments worldwide to consider expanding universal newborn screening for rare metabolic disorders. In 1997 the Massachusetts Department of Public Health developed a public process to meet this challenge. After addressing significant medical, legal, ethical, and logistical issues raised by tandem MS, Massachusetts incorporated one new disorder into the mandatory newborn screen and developed an optional pilot program for 20 additional disorders. The Massachusetts experience has wide relevance for other nations and states. As screening protocols are contemplated for entire populations—for newborns and others—it will remain essential that the public participate in an open process of reviewing the justification for and logistics of screening.

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BACKGROUND

Since establishing universal newborn screening for phenylketonuria in 1963, the Commonwealth of Massachusetts has organized and supported efforts to identify and treat significant diseases and disorders detectable and treatable in infancy.[1] Over nearly four decades, state health officials have authorized scientists and clinicians at the New England Newborn Screening Program to develop and implement new screening technologies and methods, pilot new tests for diseases, and organize a coordinated statewide system of infant follow-up and clinician support.[2–4]

In the fall of 1997, the Massachusetts Department of Public Health confronted the question of whether to take advantage of a major technological innovation in newborn screening. Addressing this seemingly simple question raised a host of thorny public health issues and led to extensive litigation. In recent months, with the benefit of this experience, Massachusetts officials have been consulted by medical, public health, and legal professionals and policy makers in other states and nations on emerging screening technologies. This article first describes the medical, ethical, and economic implications of the challenge and then reviews the process, controversies, and implementation of the Commonwealth's response.

The challenge of tandem mass spectrometry

Newborn screening for congenital disorders typically is performed on specimens of blood that are obtained by heel stick one to two days after birth, and dried onto filter paper spots. A 1995 survey in the United States demonstrated variation in the number of disorders screened for by states, from as few as three in Louisiana, South Dakota, Utah, and Washington to as many as nine in Massachusetts.[3] In addition to screening for five disorders associated with inborn errors of metabolism (phenylketonuria, galactosemia, homocystinuria, biotinidase deficiency, and maple syrup urine disease), Massachusetts screened all newborns for two endocrine disorders (congenital adrenal hyperplasia and hypothyroidism), one infectious disease (congenital toxoplasmosis), and a disorder of hemoglobin synthesis (sickle cell anemia).

Traditionally, the field of newborn screening has advanced one disorder at a time, as the technology to screen for individual conditions becomes available. In the late 1980s and early 1990s, researchers in North Carolina and elsewhere began to measure multiple metabolites at once from one newborn blood sample, using an automated process called tandem mass spectrometry (tandem MS).[6,7] Proponents claimed the technology could inexpensively and accurately screen for more than a dozen inborn errors of metabolism from a single blood sample.[8] During the summer of 1997, North Carolina launched a statewide evaluation of tandem MS in newborn screening, but no state had mandated universal tandem MS screening for all of the newly detectable disorders.

In 1997 the New England Newborn Screening Program entered its thirty-sixth year of providing universal newborn screening to all Massachusetts birthing hospitals and those in several nearby states. Based at the University of Massachusetts and located at the State Laboratory Institute of the Department of Public Health, the program facilitated comprehensive follow-up and clinician support services for infants. It also coordinated ongoing research on the prevalence of individual conditions and how best to test for them.

On October 1, 1997, a private for-profit company specializing in tandem MS wrote to the chief executives of Massachusetts birthing hospitals advertising "much more comprehensive testing . . . at a substantially lower cost . . . than you are currently paying to the New England Newborn Screening Program."[9] Several metabolic experts at local hospitals told reporters that the Department of Public Health should allow the hospitals to send specimens to the private company instead of to the New England Newborn Screening Program.[10] (There was never any barrier to the hospitals sending samples both to the New England Newborn Screening Program and to the private company.) Television news coverage of the dispute focused on the potential for saving lives by additional screening.

Despite the appealing public claim of saving children's lives while lowering costs, screening with tandem MS immediately raised several difficult questions. Among them: Was there sufficient medical and scientific evidence to justify screening for all the diseases that could now be detected? What were appropriate quality standards for newborn screening, and who should be providing screening services? To define the future of newborn screening in Massachusetts, the Department of Public Health had to confront these and other difficult questions.

A public process

In Massachusetts, state law authorizes the Commissioner of the Department of Public Health to determine which "specifically treatable genetic or biochemical disorders or treatable infectious diseases" should be screened for at birth universally, with exceptions made only for religious objection.[11] In November 1997, the Commissioner appointed the Newborn Screening Advisory Committee to develop guiding principles for

newborn screening, a list of all disorders that should be screened for, and explicit quality standards for newborn screening services.

The composition of the 17-member Advisory Committee reflected the scope and complexity of the issue being addressed. The Committee included experts in metabolic diseases (including a declared proponent of tandem MS), representatives from the New England Newborn Screening Program, a parent/consumer representative, two pediatricians, one neonatologist, one researcher, a representative of the Massachusetts Hospital Association, two officials from the Massachusetts Department of Public Health, a representative from the US Centers for Disease Control and Prevention (CDC), and a medical ethicist. It was led by the chair of the pediatrics department of a major Boston teaching hospital. Staff members from the Department of Public Health and the University of Massachusetts Medical School provided technical assistance to the Committee.

The Committee first met in December 1997. After the Department of Public Health held a public hearing and requested public comments in January 1998, the Committee met 12 times between January and June and made final recommendations in June 1998. In addition to relying on the expertise of its members and hearing from concerned citizens, the Committee reviewed the published literature on newborn screening; studied unpublished opinion surveys of metabolic experts; heard from the North Carolina and Pennsylvania state newborn screening programs (which had some experience with tandem MS); listened to parents whose children had been diagnosed with rare metabolic disorders; and interviewed several guest experts, including the founder of the private company that was offering tandem MS screening to Massachusetts hospitals. All meetings and Committee deliberations were open to the public.

Medical decisions

As a first step, the Advisory Committee set out to identify clear criteria for mandatory screening, which could then be used to determine which disorders—if any—qualified.

The Committee consulted a recent report from the United Kingdom Health Technology Assessment Programme and draft guidelines of the federally funded Council of Regional Networks for Genetic Services and the Association of State and Territorial Public Health Laboratory Directors.[12,13] After deliberation, the Committee reached consensus on nine criteria that would justify universal newborn screening for a particular condition, including treatability, test accuracy, and prevalence (Figure 1). Based on these criteria, the Committee endorsed continuation of the screening for the nine disorders already included in the Massachusetts screening panel.

The Committee next considered other disorders not screened for by the Commonwealth that potentially might meet the criteria. These included 20 disorders detectable by tandem MS (Figure 2) and one additional disorder, cystic fibrosis (CF), that several Committee members also proposed. Although screening for CF does not involve tandem MS, the Advisory Committee's broad charge to identify all disorders for screening allowed the condition to be considered.

Of the 20 metabolic disorders detectable with tandem MS, the Committee initially focused on the best-studied medium chain acyl-CoA dehyrogenase deficiency (MCAD), a disorder of mitochondrial energy production in which oxidation is blocked for medium-chain fatty acids, leading to the build-up of toxic metabolites. As a result, an affected child cannot respond normally to the stress of illness and periods of poor oral intake, and an otherwise mild illness can suddenly cause permanent neurologic damage or even death. Screening in Pennsylvania and the United King-

Figure 1. Criteria to justify mandated screening for a disorder, as developed by the Advisory Committee on Newborn Screening, 1998

- Consumer involvement in decision to mandate screening
- Availability of an accurate screening test
- Disorder is treatable and requires early treatment
- Significant, life-challenging risk of morbidity if disorder is untreated
- Reasonable price of screening test
- Significant prevalence of disorder
- Resources for and access to treatment and counseling
- Positive health benefits must outweigh risks and burdens
- Existence of mechanism for regular review of scientific and medical rationale

Figure 2. Additional disorders proposed for testing via tandem mass spectrometry

- Argininemia
- Argininosuccinic aciduria
- B-ketothiolase deficiency
- B-methyl crotonyl carboxylase deficiency
- Carnitine palmitoyltransferase II (CPT) deficiency
- Citrullinemia
- Glutaric acidemia I
- Glutaric acidemia II
- HMG lyase deficiency
- Hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome
- Isovaleric acidemia
- Long-chain hydroxylacyl-CoA dehydrogenase deficiency (LCHAD)
- Long-chain acyl-CoA dehydrogenase deficiency (LCAD)
- Medium-chain acyl-CoA dehydrogenase deficiency (MCAD)*
- Methylmalonic aciduria
- Propionic acidemia
- Short-chain acyl-CoA dehydrogenase deficiency (SCAD)
- Tyrosinemia I
- Tyrosinemia II
- Very-long-chain acyl-CoA dehydrogenase deficiency (VLCAD)

*MCAD was added to the mandatory newborn screening in the state of Massachusetts.

dom suggested a prevalence of about one in 15,000, well within the range of other screened disorders.[14,15] Early identification of children with MCAD deficiency allows parents to ensure that the child receives adequate glucose intravenously during times of poor oral intake. Screening with tandem MS for MCAD deficiency is accurate, and a recent detailed review in Great Britain concluded that the disorder "fulfills all the classical requirements for a screening programme," including treatability, test accuracy, and prevalence.[16] The Advisory Committee unanimously endorsed mandating screening for this disorder.

The Committee then turned to the other 19 disorders detectable by tandem MS. After a thorough literature review, expert consultation, and an informal national survey of metabolic experts, the Committee recognized that each of these disorders was potentially life threatening and that early identification would allow better understanding of the illness and potential preventive action.

However, the Committee also determined the need for information, as yet unavailable, on the epidemiology, range of symptoms, natural history, and treatment of these disorders. Some children identified with biochemical abnormalities at birth might later have no clinical problems (overdiagnosis bias); nonetheless, these children might be considered ill by their parents throughout childhood, and they might also have difficulty obtaining health insurance.[17–19]

For example, the Committee considered mandated screening for a group of disorders called glutaric acidemia type II. Medical understanding of these conditions, which involve defects within a metabolic pathway necessary for energy metabolism, is based largely on the description of a small number of identified cases.[20] The most severely affected newborns died soon after birth; others have been treated with diet modification and vitamin supplementation. Although these interventions have been reported to help some children, there is no clear evidence of benefit for those identified early. The Advisory Committee concluded that this disorder did not meet its criteria for mandated tests. For similar reasons, the Advisory Committee decided against mandated screening for the 18 other metabolic diseases.

The Committee next considered screening for CF, a chronic and often fatal pulmonary and gastrointestinal condition estimated to affect approximately one in 3,000 babies in the Commonwealth of Massachusetts. In October 1997, researchers from Wisconsin reported that children with CF identified by screening at birth had better nutritional outcomes after 10 years of follow-up than those identified clinically.[21] However, no pulmonary benefit had been demonstrated. In addition, there is a high false-positive rate associated with newborn screening that causes needless anxiety to several families for every child identified with CF.[22]

The Advisory Committee reviewed recent CDC recommendations suggesting that "it would be appropriate for some states to initiate pilot research projects of CF screening among newborns."[22] On the one hand, the Committee recognized that early identification would create the opportunity to improve the nutritional status of identified babies with CF; on the other hand, Committee members were unconvinced that nutritional outcome alone met the criteria for "significant life-challenging risk of morbidity" and that the screening was sufficiently accurate. As a result, the Committee did not endorse mandated screening for CF.

Legal and ethical decisions

Although the Committee determined that CF and the 19 metabolic disorders did not meet all the criteria for mandated screening, members appreciated the potential benefits of early diagnosis to children and their families. Several experts on the Committee argued that screening offered the best chance to develop effective interventions. During the deliberations, the Committee learned that the Department of Public Health has the authority beyond mandated newborn screening to conduct appropriate population-based research on newborns (with requisite safeguards for research on human subjects).

As soon as the Committee unanimously endorsed the idea of a population-based study of screening for CF and 19 metabolic diseases, the question arose of how this testing protocol would differ—if at all—from mandatory testing. For one thing, the testing protocol was provisional, and only the analysis of accumulated data could justify its continuation. Two other options were discussed: whether to seek approval from a human subjects Institutional Review Board (IRB), and whether to obtain consent from parents for the investigational screening. According to federal regulations, IRB approval is needed for all "research involving human subjects," with *research* defined as "a systematic investigation (that is, the gathering and analysis of information) designed to develop or contribute to generalizable knowledge."[23] Some Committee members expressed concern that an IRB might delay implementation of the testing protocol and require so many revisions as to make the screening impractical. Nonetheless, most of the Committee members agreed that a population-based study of newborns for CF and 19 metabolic disorders was indeed research on human subjects. The Committee thus recommended that the newborn screening laboratory develop two pilot protocols that would be subject to IRB approval: a CF screening protocol and a protocol for the 19 rare metabolic disorders detectable by tandem MS.

The question of whether parental consent was advisable, necessary, or required produced tremendous conflict within the Committee. Some members pointed out that consent had not been required with the initial introduction of population screening for phenylketonuria in 1962, even though the implications and consequences of universal screening were not well understood at the time. These members also questioned whether new parents would be able to understand the intricacies of screening well enough to make informed judgments. In opposition to this position, the consumer member of the advisory group urged the Committee to allow parents to refuse screening for the investigational tests. After a long debate, most of the Committee members recommended that the organization performing the investigational screening consult with the IRB and the Committee to determine "what type of consent should be obtained and/or what type of information should be provided to the parent or guardian of the newborn."

A final issue raised by the use of investigational protocols was the question of who would review the results to determine whether screening for each of the disorders under consideration should be mandated or discontinued altogether. The Committee unanimously recommended that a permanent advisory committee be established to review the study results, make recommendations on testing, and serve in an ongoing advisory role to the Commissioner on new developments in the field of newborn screening.

Logistical issues

At the same time as the Committee was making disorder-specific recommendations, it was also reviewing quality standards for newborn screening. The goal of this review was to use these standards to guide decisions about what types of systems or organizations to entrust with the screening. The Committee began by reviewing existing technical guidelines from the Counsel of Regional Networks for Genetic Services and legal standards under the Clinical Laboratory Improvements Amendments of 1988.[24]

The Committee also reviewed the definition of *follow-up* in a comprehensive screening system. It became clear that, ideally, program staff members would contact and educate pediatricians and neonatologists, provide for appropriate referral, and, if necessary, find the child and inform the family—all while protecting data confidentiality, monitoring quality assurance, and conducting research to improve the screening system.

The New England Newborn Screening Program detailed for the Committee its quality assurance protocols for all levels of testing and follow-up, including its use of birth records to identify children who may not have been screened.

Drawing on these standards and its own expertise, the Advisory Committee developed four guiding quality principles: clear responsibility for the chain of custody of the test blood sample; a system of quality assurance/quality control; strict confidentiality provisions; and clear standards for storing, labeling, use of, and research on blood specimens. To make these standards operational, the Committee recommended that the agency responsible for running the newborn screening program present data on the program annually to a permanent Advisory Committee (Figure 3).

While the Committee was conducting its final deliberations in the spring of 1998, the New England Newborn Screening Program at the University of Massachusetts Medical School obtained tandem MS technology for expanded universal newborn screening. The Program indicated that screening for the full battery of both the mandated and pilot tests to be recommended by the committee—including comprehensive follow-up services—would be included in a one-time fee of $42 per newborn. A letter sent by a private company specializing in the new technology, which had offered its services to birthing hospitals for the cost of $25 per newborn, did not make clear whether the fee covered the full range of screening and follow-up services.

During the course of its deliberations, the Committee acknowledged that only the New England Newborn Screening Program had a record of proven comprehensive service to families and clinicians in Massachusetts. The Committee also noted the advantages of using a public system that is accountable to public officials and ultimately to voters. It is secure, with safety regulations and employees directly under public control. It is also legally authorized to conduct the types of research necessary to improve testing methods and screening algorithms for the benefit of the Commonwealth's newborns. Such a system would also promote major public health goals in synchrony with the Department of Public Health's mission and mandate to share information on screening with other states and countries. For all these reasons, the Committee endorsed the continuation of screening through the New England Newborn Screening Program.

To ensure accountability and universality, the Committee recommended that hospitals continue to be required to send samples to the Program. This recommendation, however, precluded neither the Program nor the Department from later choosing to subcontract with a private laboratory for particular services. Nor did it prevent hospitals from sending additional samples directly to private laboratories for these or other tests.

Implementation

The Department incorporated the Advisory Committee's recommendations into proposed regulations in July 1998. The proposed regulations mandated the 10 required tests (the nine previously mandated plus MCAD), established the pilot studies for CF and the 19 rare metabolic diseases, named the Department of Public Health as the receiver of newborn screens, and provided for a permanent advisory committee whose membership would include parents and other consumers.

At this late stage, the method for obtaining informed consent from parents for the pilot studies had not yet been determined. The New England Newborn Screening Program, with guidance from the general counsel of the Department of Public Health, proposed an "informed dissent" protocol in which information and counseling would be made available along with an opportunity to refuse the investigational screening. This protocol met the goal of allowing any parent to refuse optional screening for CF and the 19 rare metabolic diseases; it also avoided the practical difficulty of obtaining and keeping signatures for the thousands of patients screened.

Approval of the protocols for the two pilot studies that authorized testing for CF and the 19 metabolic diseases was obtained from the Advisory Committee, from the Department's IRB, and from the IRB at the University of Massachusetts in the late summer of 1998. The regulations, officially approved by the Public Health Council, established that expanded screening would begin on February 1, 1999.

To implement both the new mandated and investigational screening, staff of the New England Newborn Screening Program provided in-service training at all birth units in more than 55 Massachusetts hospitals; presented the protocols at professional conferences of perinatal practitioners statewide; developed (and translated into eight foreign languages) written educational materials for parents and providers; redesigned lab slips used for the collection of blood and demographic information; notified every obstetrician, pediatrician, and family provider in the state about the program; and developed a web site for parents and providers (http://www.umassmed.edu/nbs/).[25]

By the fall of 2000, approximately 97% of parents

Figure 3. Quality measures developed by Advisory Committee on Newborn Screening for Massachusetts

Goal	*Measure*
Screening for all newborns for diseases and disorders as directed by the Department	Percentage of newborns screened Percentage of positive test reports for which follow-up is completed
Quality assurance of newborn screening program	Ongoing, prospective evaluation of program operations using consensus criteria developed by Advisory Committee
Specimen collection and transportation	Percentage of satisfactory specimens from newborns received by the screening laboratory
Timely reporting of accurate test results	Percentage of children screened and test reports received by hospital and physician within critical treatment window Repeat specimens obtained quickly
Referral to appropriate care	Percentage of newborns with positive laboratory tests followed to confirm screening results Percentage of newborns referred to clinical specialists for early intervention, if appropriate
Access to post-screening counseling for families of affected newborns	Percentage of families receiving timely post-screening counseling
Surveillance of disorders, evaluation of data and coordination of screening information so as to inform health policy	Public and professional review of program outcomes measured against benchmarks established by the Massachusetts Department of Public Health
Confidentiality and security of test data and specimen storage	No breaches of data confidentiality Specimen archives maintained and any proposed use of stored specimens reviewed for appropriateness
Stability and dependability of newborn screening services	Program operations responsive on a 24-hour and 7-day per week basis
Pre-screening information for parents, and communication of feedback	Educational materials continuously updated and made available to parents through multiple means of communications
Access to research findings, screening information, test methodologies, and technology for newborn screening	No impediments to open access to information and technology related to newborn screening

had participated in the investigational screening, allowing the Program to collect population-based data. A representative of the largest Massachusetts birthing hospital reported anecdotally that the consent process for the expanded state screen had given nurses in maternity units an opportunity to talk to parents about a host of issues related to newborn care. The Department of Public Health has established a permanent Newborn Screening Advisory Committee.

Litigation

After the Advisory Committee endorsed screening by the New England Newborn Screening Program, the private company that had written to Massachusetts

hospitals in the fall of 1997 sued the Commonwealth of Massachusetts on the grounds that the state had engaged in monopolistic behavior with regard to newborn screening in violation of the Sherman Anti-Trust Act. The case was decided in favor of the Commonwealth in US District Court on December 8, 1998.[26] The company appealed the ruling, on July 14, 1999, and the First Circuit Court of Appeals again responded in favor of the Commonwealth.[27] In October 1999, the private company requested that the United States Supreme Court hear an appeal. That request was denied on December 13, 1999, thus ending the legal challenge.

DISCUSSION

The authors of two reviews of newborn screening initiatives have criticized "extemporaneous" policy making, which occurs largely in response to an assortment of unpredictable legal and economic stimuli, and praised a logical, evidenced-based path to decisions on mandated screening and pilot studies.[28,29] The Massachusetts experience demonstrates that the line between the two approaches is not always crystal clear. Newborn screening policy does not develop in a vacuum. The decision to mandate screening for a particular disorder is the product of a regulatory and political process that can be profoundly influenced by both public and private interests.

For years, Massachusetts relied on experts from its screening program to advise the Commissioner on new technologies. Yet when faced with this latest challenge, the Department created a public process to help it develop newborn screening policy in recognition of the vast implications of population-based screening for the state's infants and families. Despite some initial disagreement, the Advisory Committee reached near-consensus over a six-month period on a number of key issues: criteria for mandated screening, criteria for quality screening, disorders to be screened, the organization to perform the screening, a research protocol, and informed consent. The Massachusetts experience anticipated many of the recommendations later made for state agencies by the Task Force on Newborn Screening, a professional group convened by the American Academy of Pediatrics.[30]

One key to the ability to develop a credible policy in Massachusetts was public involvement in and access to the Advisory Committee. The Committee included members from all interested sectors, including a consumer representative and several metabolic experts who had publicly criticized the New England Newborn Screening Program. Public hearings and Committee presentations brought additional opinions of health officials from other states, private laboratories, and affected families to bear on the policy process. These steps gave the Committee's work credibility and led to a general appreciation of a public system of newborn screening—one that continues to invite and respect consumer input and reviews data to optimize care of newborns in the Commonwealth of Massachusetts.

A second key element of the Massachusetts experience was the broad charge given to the Advisory Committee by the Commissioner. An initial consensus on appropriate criteria for screening eventually led to agreement on which disorders to include. Similarly, the Committee's development of quality guidelines led to the recognition of the intricacies and importance of follow-up and ongoing research. This understanding, in turn, facilitated decisions about what services were essential and what type of system would best provide those services.

The creation of explicit newborn screening criteria and quality measures was essential to the Committee's shaping of an appropriate public policy. It can be difficult to explain to the public and press that more screening is not always better. Initial newspaper and television reports in the fall of 1997 focused nearly exclusively on the potential that the current public screening program might miss a child with a devastating illness. Only after careful deliberation and research, however, did it become clear to most of the Committee members that many of the metabolic disorders detectable by tandem MS did not yet meet the criteria of treatability, test accuracy, and prevalence. The development of a research protocol then allowed the Committee to balance the potential benefit to families and the importance of gaining information on these disorders against the lack of justification for mandated screening. This balance led to a protocol that gave families the right to dissent from testing.

In the spring of 2000, the Massachusetts Department of Public Health moved to incorporate lessons learned from this experience into future policy making on newborn screening. Recognizing the potential for more consumer input (and its benefits), the permanent Newborn Screening Advisory Committee now has four parents as members. One of the Committee's goals is to review available data to identify emerging challenges proactively and respond with consensus recommendations. However, this ideal may not always be attainable. What is most important is the existence of an effective and fair public process to advise on difficult and controversial decisions.

Given the complexities of the Massachusetts response to the challenge of tandem MS, it is no wonder that screening policies nationwide are as diverse as the

states themselves. In a recent survey of directors of state newborn screening programs, one indicated that changing the state screen in his or her state was "virtually impossible," two indicated it was "exceedingly difficult," 22 reported it was "slower than optimal," 25 said change is "appropriately careful and deliberate," and two reported that it was "dynamic and timely."[29] Another recent survey found that only 26 of 51 state screening programs have advisory committees that include consumer representatives.[5]

As the twenty-first century begins, medical science must continuously improve its capacity to prevent or mitigate disease through screening and early treatment. It is essential that the public participate in an open process of reviewing the justification for and logistics of screening. Even—and especially—in an era of genetic testing and molecular diagnosis, such a process is the essence of public health.

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