ARTICLE

Integration of New Genetic Diseases into Statewide Newborn Screening: New England Experience

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Using a data set of newborn screening specimens tested by the New England Newborn Screening Program (NENSP) between January 1999 and February 2003, we analyzed the number of infants with positive newborn screening results and determined how many positive screening results were due to a recent multiplex expansion of services in some of the states. We found that for the subset of the 4-year cohort for which there was a 233% increase in the number of disorders screened (from 9 to 30 disorders), there was a 31% increase in the number of affected infants identified by the screen. We project that if all states in the program expanded their services and if the incidence of disorders is similar across states, there would be an observed 45% increase in the number of infants detected by the screen and a 43% increase in the number of infants for whom the screening algorithm would require some contact with the infants' health care provider. Furthermore, of those requiring contact, we project a 300% increase in the number of screened-positive infants who would be referred to tertiary care centers for a diagnostic evaluation. Increased contact with the medical community from additions to newborn screening as demonstrated in this report emphasizes the need for an approach in which the newborn screening program assures coordinated communications between birth units, laboratory, primary health care providers, and specialists.

KEY WORDS: newborn screening; newborn screening expansion; tandem mass spectrometry; cystic fibrosis screening

INTRODUCTION

Newborn screening programs provide opportunity for early identification and treatment of infants who have disorders that otherwise would go unrecognized prior to irreversible clinical damage. This early opportunity is possible because indicators of disorders are detectable in the dried blood spot (DBS) specimens that are collected universally from the newborn population at approximately 2 days of age during a presymptomatic period. Newborn screening as a successful population-based public health service was first demonstrated in Massachusetts in 1962 when statewide screening for phenylketonuria (PKU) was implemented [Macready, 1963] after Guthrie's 1959 demonstration of technical feasibility.

In Massachusetts, unprecedented 1963 legislation firmly established newborn screening as the first population-based genetic screening applied universally [MGLc111 4E and 110A]; the preventive screening was mandated, regulated by state public health officials. Other states soon adopted the preventive public health model, and as tests for indicators of other biochemical genetic disorders were validated, more treatable single-gene disorders were added to the panels tested by newborn screening programs. Demonstration that congenital hypothyroidism could be detected by an assay for thyroxine (T4) [Dussault et al., 1975] opened the door to newborn screening for disorders not traditionally considered to be genetic (complex genetic and multifactorial disorders). Today, statewide newborn screening programs provide services for detecting a variety of disorders that are amenable to pediatric clinical interventions established by specialists in biochemical genetics, endocrinology, hematology, infectious disease, or pulmonology.

Table I shows a chronology of Massachusetts' additions of disorders to its newborn screening program and our experienced-based incidence data. From the 1960s through the mid 1990s, the public health expansion of newborn screening was driven by the availability of screening tools and whether the disorder fit the criteria set by the World

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TABLE I. Chronology of Provision of Services to 5 New England States by the New England Newborn Screening Program★

		States (approximate yearly birth cohort) and year screening began[a]				
Disorder	Incidence	Massachusetts (80,000)	Maine (14,000)	Rhode Island (14,000)	New Hampshire (14,000)	Vermont (6,000)
Phenylketonuria	1:15,000	1962	1976	1976	1983	1989
Maple Syrup Urine Disease	1:250,000	1963	1976	1976	1983	1989
Galactosemia	1:100,000	1964	1976	1976	1983	1989
Homocystinuria	1:500,000	1968	1976	1976	1983	1989
Congenital Hypothyroidism	1:2,200	1976	1976	1976	1976	1989
Congenital Toxoplasmosis	1:27,800	1986	Not done	Not done	1988	Not done
Hemoglobinopathies	1:2,900	1990	2001	1990	Upon request by physician	1996
Congenital Adrenal Hyperplasia	1:19,200	1990	1998	1994	Not done	(2003)[b]
Biotinidase Deficiency	1:42,000	1992	1999	1994	Not done	1992
MCADD	1:21,000	1999	1999	2002	Not done	(2003)
Optional Met Panel (MET 19)[c]	1:11,400	1999	2001	Not done	Not done	(2003)
Optional CF	1:2,900	1999	Not done	Not done	Not done	Not done

★New England Newborn Screening Program of the University of Massachusetts Medical School.

[a]Actual month and day screening began varies by state and condition screened.

[b]Anticipated start date.

[c]MET 19 refers to the 19 disorders listed in MA Regulations. Since promulgation of regulations, greater understanding of metabolic pathways indicated that LCAD was not a disorder. SCAD, short-chain acyl-CoA dehydrogenase deficiency; LCHAD, long-chain hydroxy-CoA dehydrogenase deficiency; CPT II, carnitine palmitoyl transferase deficiency; VLCAD, very-long-chain acyl-CoA dehydrogenase deficiency; GA II, Glutaric Acidemia II; PA, Propionic Acidemia; MMA, Methylmalonic Aciduria; IVA, Isovaleric Acidemia; GA I, Glutaric Acidemia I; BKT, ß-Ketothiolase Deficiency; MCC, ß-Methyl Crotonyl Carboxylase; HMG, HMG Co-A Lyase Deficiency; Tyr I, Tyrosinemia I; Tyr II, Tyrosinemia II; ASS, Citrullinemia; ARG, Argininemia; HHH, HHH Syndrome; ASL, Argininosuccinic Aciduria.

Health Organization (WHO) [Wilson and Jungner, 1968]. The occasional new addition allowed for the medical community's education and adjustment to the new addition during interim periods. By the late 1990s, available screening tools offered technologic opportunities [Millington et al., 1990; Rashed et al., 1997; Naylor and Chace, 1999] for additions of multiple disorders simultaneously (multiplex expansion) and for incorporation of assays that would yield detailed genotypic data [Gregg et al., 1993; Comeau, et al., in press]. In several circumstances, technologic advances in testing outpaced medical knowledge, resulting in heightened sensitivity about the application of WHO criteria and posing challenges for cooperation among parent advocacy groups, clinical specialists, and public health scientists. Atkinson et al. [2001] describe the Massachusetts Department of Public Health policy approach to such challenges. Similar approaches, including contribution by a newborn screening advisory committee to decision making about expanded screening, have been adopted in other states in New England and elsewhere. Thus, increasing numbers of states in the United States are deliberating or implementing an expansion that is likely to be multiplex. In this report, we describe the New England Newborn Screening Program's (NENSP) approach and experience with implementation of 1) multiplex expansion and 2) report of genotypic data. We report on the implications for medical services in terms of rates, numbers, and types of patient contacts resulting from expansion of newborn screening.

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METHODS

Data Evaluation and Analysis

All data were centralized at the NENSP. Analytical data from specimens of infants

who had attained a weight of 2,500 g and who were born in Massachusetts, Maine, New Hampshire, Rhode Island, or Vermont between January 15, 1999, and January 31, 2003, were included in the specimen data set to be analyzed. For each disorder, analytical data were available for evaluation as of the date that a particular state implemented statewide screening using the NENSP for provision of services (Table I). Preset criteria matching the current NENSP screening and follow-up algorithms and the current NENSP working case definitions were applied to the specimen data set for each disorder. From that application, we projected the number of infants who would screen positive, who would need further diagnostic evaluation, and who would be counted as affected by current algorithms and definitions. All incidence data were converted to incidence per 500,000 births to facilitate comparison between disorders, some of which were less frequent than 1/500,000.

Laboratory Implementation of Multiplex Expansion

Expansion that included use of tandem mass spectrometry (MS/MS)

The laboratory screening algorithms used for disorders screened by MS/MS (includes medium-chain acyl Co-A dehydrogenase deficiency (MCADD) and an optional panel of 19 metabolic disorders (MET 19) in addition to the preexpansion disorders, PKU, maple syrup urine disease (MSUD), and homocystinuria (HCU)) are detailed in Zytkovicz et al. [2001]. In brief, for each type of requisition received by the laboratory, the tandem mass spectrometer was programmed for a set of rules that determined the specific set of markers to be assayed. For example, requisitions from states that had not yet expanded to screening for disorders of fatty acid oxidation, organic acids, or urea cycle were assayed for relevant amino acids but not for acylcarnitines. When a requisition showed MCADD to be the only postexpansion disorder for which screening was requested, MS/MS was programmed for acylcarnitine assays, including the 8-carbon (C8) compound octanoylcarnitine, but not, for example, the 3-carbon compound (C3) propionylcarnitine. Likewise, requisitions for multiplex metabolic expansions were programmed to detect analytes associated with the disorders on the list, as opposed to a full scan of all masses.

Expansion that included use of DNA markers

The 1999 Massachusetts expansion included optional newborn screening for cystic fibrosis (CF). We used a modification of the two-tiered immunoreactive trypsinogen (IRT)/DNA protocol described for the state of Wisconsin [Gregg et al., 1993]. The primary modification was the inclusion of assays for 27 (increased from 1) mutations in the CF transmembrane conductance regulator *(CFTR)* gene [Comeau et al., in press]. In brief, all specimens with requisitions for CF screening were tested for IRT, and specimens with IRT concentrations in the top 5% were tested for 27 *CFTR* mutations.

The screening algorithm for the disorders, MCADD and galactosemia, also had a DNA component. All specimens with requisitions for MCADD screening were tested for C8. Specimens with C8 concentration greater than or equal to 0.5 μmol/l were tested for the predominant MCADD mutation. All specimens with requisition for galactosemia screening were tested for galactose. All specimens with total galactose $\geq$6 mg/dl (top 5%) were tested for the enzyme galactose 1 phosphate-uridyl transferase (GALT). Reduced or absent enzyme activity on two independent specimens prompted DNA analysis for 1 of 3 GALT gene mutations.

Follow-Up Protocols for Positive Screening Results

Overview

For each infant whose specimen showed a positive screening result, the result was reported to the infant's health care provider with recommendations for next-step action and, when relevant, communication of projected relative risk based on the screening result. Each positive screening result was associated with a specific action by NENSP follow-up personnel. When the screening result was markedly positive, or the disorder-specific risk of immediate clinical progression was high, or the infant had additional significant risk factors, next-step action recommended by NENSP in a telephone consult required additional laboratory tests to be obtained by the primary care provider and/or direct referral to a specialist for diagnostic workup. When the screening result was borderline or the disorder-specific risk of clinical progression was low, next-step action was recommended for obtaining another DBS specimen. All infants with positive screening results were tracked by the NENSP until the diagnosis was ruled out based on current working case definitions, or when it was confirmed, through to treatment.

Follow-up when screen included DNA assays

NENSP protocol recommended that diagnostic evaluation and genetic counseling be offered to the family of any infant whose positive screening result included detection of a mutation. For CF, infants in whom one or two mutations were detected, or with an IRT concentration in the top 0.2% (even in the absence of any detected mutation), were considered to have positive screens requiring referral to a CF center. For MCADD, infants with one or two mutations detected by the screen, or with C8

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≥0.8 μmol/l, or with serial specimens above 0.5 μmol/l were considered to have positive screens requiring referral to a metabolic center. For galactosemia, infants with one or more mutations detected by the screen or with continued high galactose (>14 mg/dl) and/or absent enzyme were considered to have positive screens requiring referral to a metabolic center.

The delivery of genetic counseling services varied by disorder. For CF, all infants with a positive CF screen were sent to a CF center for diagnostic evaluation by sweat testing. CF physician specialists only consulted directly on the infants with positive sweat tests (8% infants referred). The recommendation for genetic counseling was targeted to all families of infants whose diagnostic evaluation showed the infant to be a carrier because these families will not have the ongoing support of the tertiary care team. In contrast, for metabolic evaluations, all infants meeting criteria for referral had a diagnostic evaluation by a physician specialist that included genetic counseling by that specialist regardless of diagnostic outcome.

Assurance of Follow-Up and Collaboration with Specialists

Prior to implementation, the NENSP initiated collaborative agreements with specialists who would play an integral role in the diagnosis and management of infants identified by the screen. In anticipation of the large number of infants who would need sweat testing and whose families would need genetic counseling, all five Massachusetts CF center directors participated in the planning and follow-up algorithms that would be recommended for infants with positive screens. Likewise, for the 20 new metabolic disorders and in anticipation of the challenges to diagnostic evaluation in the absence of gold standards for asymptomatic infants, several Massachusetts metabolic specialists participated in the evaluation of screening and outcome data in order to optimize the screening program's follow-up algorithms, interpretation, and communications about these rare disorders. NENSP retained two metabolic specialists for a total 70% full-time equivalent for the first year. Since then, directors of two large clinics were retained as consultants and meet every other week with NENSP staff; all MA metabolic specialists are invited to annual working meetings and most metabolic specialists participate in the New England Consortium [Albers et al., 2001].

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RESULTS

Case Detection

Table II shows that two disorders (congenital hypothyroidism and sickling disease, both of which were listed on the preexpansion screening panel) accounted for almost two-thirds (64%) of the affected infants identified by the NENSP during this period (Note: These two disorders would have accounted for 83% of all cases had no expansion occurred.) The remaining seven disorders that were screened preexpansion accounted for an additional 13% of diagnosed cases. Finally, 24% of cases detected were associated with the up to 21 disorders that were added to Massachusetts, Maine, and Rhode Island screens in 1999 or later. Because our data set covers a period of rapid state policy development, the numbers of disorders included in various state panels underwent several changes throughout the analyzed period. In order to simplify the presentation, Table II also presents all data in terms of rates per 500,000 screened. Data presented below is expressed at these rates. If the observed rates in the subset that were screened were generalizable across all states and if all states had implemented screening for the same disorders and on the same timeline as Massachusetts, the disorders added in the 1999 Massachusetts expansion would have accounted for 30% of all cases detected. Under those assumptions, the 233% increase in the number of disorders from 9 to 30 would have resulted in a 45% increase in the number of affected infants identified by the screen. Most of the infants identified with one of the 21 disorders added through expansion (151/218) would have been infants with the single disorder CF, which accounts for the third highest incidence and brings the cumulative case detection from 56% for two disorders to 78% for three disorders, including CF. Expansion for 20 disorders would be responsible for 10% of total detected disorders. Of the 67 non-CF infants identified by multiplex expansion in a birth cohort of 500,000, 23 would have MCADD and 44 would have one of 11 of the MET 19 disorders (Table II). To date, no infants have been identified with 8 of the MET 19 disorders, with tyrosinemia being the one disorder accounting for the most false positive screens (120/667 and 6/190 specialist referrals).

Additional Contact with Medical Community for Screen-Positive Infants

Table II also shows the projected number of infants in a cohort of 500,000 newborns whose positive screen would require additional follow-up to ascertain whether the infant is affected. Simultaneous expansion from screening for 9 disorders to 30 disorders would yield an immediate 43% increase in the number of infants for whom the algorithm would require some contact with the infant's health care provider (an additional 2,728 screen-positives per 500,000 births). Of these new contacts by the screening program, 72% would be due to infants who screened positive for CF. Overall,

TABLE II. Estimated Number of Infants Who Would be Identified by Screening With Application of Current New England Newborn Screening Program Screening Algorithms and Case Definitions★

Disorder	N[a]	Cases observed in NENSP specimen dataset (n)	Screen + per 500,000	Specialist referral per 500,000	Case incidence/ 500,000	Screen + per case	Specialist referral per case	% Total pre-expansion cases	% Total post-expansion cases
Congenital hypothyroidism	476,514	218	3,488	612	229	15:1	3:1	47	33
Sickling disorder	419,476	141	168	168	168	1:1	1:1	35	24
CAH	401,241	21	1,089	65	26	42:1	3:1	5	4
Toxoplasmosis	332,312	15	161	93	23	7:1	4:1	5	3
PKU	472,254	19	293	59	20	15:1	3:1	4	3
BIO	415,247	10	119	17	12	10:1	1:1	2	2
Galactosemia	476,410	4	573	83	4	137:1	20:1	1	1
MSUD	472,254	2	187	13	2	89:1	6:1		
HCU	472,255	1	221	8	1	209:1	8:1		
Pre-expansion		431	6,300	1,118	485	13:1	2:1		
MCADD	**349,756**	**16**	**87**	**73**	**23**	**4:1**	**4:1**		**3**
Cystic Fibrosis	**298,706**	**90**	**1,974**	**1,974**	**151**	**13:1**	**13:1**		**21**
MET 19	**318,535**	**28**[b]	**667**	**190**	**44**	**15:1**	**4:1**		**6**
Post-expansion		565	9,028	3,354	703	13:1	5:1		

★New England Newborn Screening Program of the University of Massachusetts Medical School. Bold indicates disorders from 1999 expansion. Retrospective analysis actual laboratory data from specimens of infants weighing ≥2500 g and born between 1/31/99 and 2/1/03.

[a]N = number of infants in specimen dataset. Numbers vary by disorder because states served by NENSP use different panels and dates of implementation.

[b]Four infants with CPTII deficiency (incidence rate/500,000 or IR = 6); one infant with LCHAD (IR = 2); six infants with SCAD (IR = 9); six infants confirmed and two pending with VLCAD (IR = 9–13); two infants with IVA (IR = 3); one infant with MBCD (IR = 2); two infants with 3MCC Def (IR = 3); two infants with MMA (IR = 3); two infants with PA (IR = 3); one infant with Argininemia (IR = 2); one infant with ASA Synthetase Def (IR = 2).

the positive predictive value of the screen would remain steady at about 7.7% or 13 positive screening results for every case detected.

The number of screened-positive infants referred to a tertiary care center would triple with the expansion, largely accounted for by the 100% referral rate for infants with a positive CF screen. Unlike the other disorders that were added to the Massachusetts list in 1999, the CF diagnostic evaluation, case definition, and prognosis were familiar to the primary care provider, and so provider education focused on interpretation of the screening test. In contrast to CF, few health care providers had experience with any of the 20 new metabolic disorders, and health care provider education about the disorders upon report of a positive screen was essential. Projected referrals to a metabolic center increased by 146% (180/500,000 preexpansion vs. 443 postexpansion). Overall, multiplex MS/MS expansion changed the case-to-referral ratio from 1:2 to 1:5, lowering the positive predictive value from 50% to 20%.

Referrals for genotypic assays used in newborn screening

Table III shows the number of infants for whom one of the GALT or MCADD mutations was detected by screening. Each of the four infants with classical galactosemia had biochemical screening indicators that automatically prompted direct referral to a metabolic center. Of the 16 infants with MCADD, all had biochemical screening indicators that prompted direct referral to a metabolic center. In addition to the 20 infants affected with either galactosemia or MCADD, another 29 unaffected infants (18 for galactosemia and 11 for MCADD) had biochemical indicators yielding a positive screen that required referral to a metabolic center regardless of genotypic data. Furthermore, among the 122 unaffected infants whose screen-positive biochemical results did not require referral to a metabolic center but prompted DNA analysis, 50% subsequently required referral to a metabolic center after screening detection of a mutation associated with the disorder.

In contrast to the low number of metabolic screenings that prompted DNA analysis, a total of 14,935 infants had first-tier CF screens that prompted DNA analysis. Of these, 13,756 had no

TABLE III. Screening and Follow-up Data for Infants Whose Screening Report Included Recommendation for Referral to a Metabolic Center by the New England Newborn Screening Program Because the Screening Algorithm Showed a High-Risk Biochemical Profile or Showed Detection of a Mutation

Disorder	Biochemical profile	n	Mutation data obtained from screen	DNA from follow-up testing	Outcome
Galactosemia	High risk	2	Q188R/Q188R	Not done	Classical
	High risk	1	One copy Q188R	TBD[a]	Classical
	High risk	1	One copy N314D	TBD	Classical
	High risk	18	None detected	Not done	Unaffected
	Low risk	42	Q188R/N314D or One copy of Q188R or N314D or S135L	Not done	Unaffected
MCADD	High risk	7	985A > G/985A > G	Not done	MCADD
	High risk	4	One copy 985A > G	One copy other	MCADD
	High risk	1	None detected	Other/other	MCADD
	High risk	3	One copy 985A > G	TBD	MCADD
	High risk	1	One copy 985A > G	None detected by sequencing	MCADD
	High risk	11	None detected	TBD	Unaffected
	Low risk	34	One copy 985A > G	TBD	Unaffected

*New England Newborn Screening Program of the University of Massachusetts Medical School.
[a]To be determined.

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detectable mutation and screened negative. Of the 1,179 infants referred to a CF center, 1,089 were sweat negative and are considered unaffected. Of these, 847 were shown to be unaffected carriers and their families were offered genetic counseling. Of the 90 affected infants, only 3 had none of the mutations included in the screen and these 3 were referred to a CF center on the basis of IRT in the top 0.2%. As expected for a high-incidence disorder like CF, tests ordered after genetic counseling yielded information that both partners in the 5% of the counseled couples were carriers of the disorder [Wheeler et al., 2001; our own unpublished observations].

DISCUSSION

Simultaneous addition of 21 disorders to the panel for which a large cohort of New England newborns were screened provided opportunity for identification of more infants with a variety of presumably treatable disorders. The number of affected infants who benefited from the recent multiplex expansion of newborn screening was not directly proportional to the number of new disorders, and this can be attributed to the particularly low incidence rate for many of the disorders included in the multiplex expansion.

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Multiplex testing by MS/MS allowed identification of infants with 12 disorders that previously would not have been identified until clinical presentation; $\frac{1}{3}$ of these infants had one disorder, MCADD. Incorporation of DNA testing in newborn screening algorithms can increase specificity of the screen when used to rule out possible screen positives (as for CF); it also increases the number of referrals for genetic counseling, especially when used as a supplemental assay (as for MCADD or galactosemia).

The one disorder (CF) that yielded the highest number of affected infants was added as a single disorder using technology directed at detecting biochemical and genetic indicators of CF. Newborn screening for CF yielded a high rate of positive screens (second only to screening for congenital hypothyroidism) and referral to a CF center. Because CF centers were involved in the planning of the follow-up protocol, it was

possible to ensure prompt standardized diagnostic sweat testing and genetic counseling for the relatively high number of carriers identified by the screen.

The other 20 disorders (MCADD and MET 19) added as a multiplex expansion using a single technology (MS/MS) showed a significantly lower number of positive screens than CF, and much fewer of the infants who screened positive required diagnostic evaluation at a metabolic center. However, significant educational time by follow-up personnel in the screening program per report was required. A key component of the successful implementation was ongoing andinteractive consultation between the screening program and metabolic specialists allowing for effective result interpretation and other communication support to the primary care provider.

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Integration of new disorders into statewide newborn screening programs has a demonstrated record of successful implementation dating back to the 1960s. Many of these disorders follow classical Mendelian inheritance for single-gene disorders providing a long-term demonstration of acceptance by the medical community and general society of (at least some) population-based genetic screening. Success of newborn screening is fulfilled only when the alert from the screening laboratory is recognized and accepted by the medical community and the affected infant is appropriately treated. Increased contact with the medical community from additions to newborn screening as demonstrated in this report emphasizes the need for an approach in which the newborn screening program assures coordinated communications between birth units, laboratory, primary health care providers, and specialists. Such coordinated communications, particularly as they relate to 1) communication by the program of projected relative risk for a particular infant's screening result and 2) prearrangement by the program of referral protocols for diagnostic evaluation and genetic counseling in specialty centers, are key components to maintaining necessary cooperation from the medical community and confidence in this public health service. The numbers of contacts with the medical community will increase with every expansion. The complexity of contacts will increase as newborn screening programs incorporate screening for ever more rare disorders and as they integrate genotypic data. As the programs grow, newborn screening programs have a responsibility to investigate technology that maximizes identification of infants at risk with maximum specificity and to minimize the burden on the medical community receiving screening results with timely, coordinated communications.

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