

# Effect of Expanded Newborn Screening for Biochemical Genetic Disorders on Child Outcomes and Parental Stress

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**R**OUTINE NEWBORN SCREENING IS required practice for newborn care throughout the United States. It began as screening for a single biochemical genetic disorder, phenylketonuria, in the 1960s.<sup>1</sup> Over the years, congenital hypothyroidism and a few additional metabolic disorders were included.<sup>2,3</sup> Traditionally, testing for each disorder required a separate test and a separate disk punched from the newborn dried blood filter paper specimen. The application of tandem mass spectrometry to

**For editorial comment see p 2606.**

**Context** Tandem mass spectrometry now allows newborn screening for more than 20 biochemical genetic disorders. Questions about the effectiveness and risks of expanded newborn screening for biochemical genetic disorders need to be answered prior to its widespread acceptance as a state-mandated program.

**Objectives** To compare newborn identification by expanded screening with clinical identification of biochemical genetic disorders and to assess the impact on families of a false-positive screening result compared with a normal result in the expanded newborn screening program.

**Design** Prospective study involving an inception cohort of newly diagnosed children.

**Setting** Massachusetts, Maine, and a private laboratory in Pennsylvania with expanded newborn screening; other New England states with limited screening.

**Participants** Families of 50 affected children identified through expanded newborn screening (82% of eligible cases); 33 affected children identified clinically (97% of eligible cases); 94 screened children with false-positive results (75% of eligible cases); and 81 screened children with normal results (63% of eligible cases).

**Main Outcome Measures** Child's health and development and the Parental Stress Index.

**Results** Within the first 6 months of life, 28% of children identified by newborn screening compared with 55% of clinically identified children required hospitalization ( $P = .02$ ). One child identified by newborn screening compared with 8 (42%) identified clinically performed in the range of mental retardation ( $P < .001$ ). Mothers in the screened group reported lower overall stress on the Parental Stress Index than mothers in the clinically identified group ( $z = 3.38$ ,  $P < .001$ ). Children with false-positive results compared with children with normal results were twice as likely to experience hospitalization (21% [ $n = 20$ ] vs 10% [ $n = 8$ ], respectively;  $P = .06$ ). Mothers of children in the false-positive group compared with mothers of children with normal screening results attained higher scores on the Parental Stress Index ( $z = 4.25$ ,  $P < .001$ ) and the Parent-Child Dysfunction subscale ( $z = 5.30$ ,  $P < .001$ ).

**Conclusions** Expanded newborn screening may lead to improved health outcomes for affected children and lower stress for their parents. However, false-positive screening results may place families at risk for increased stress and parent-child dysfunction.

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newborn screening now provides the possibility of screening for many treatable disorders with a single evaluation, requiring only a single disk of the newborn blood specimen.<sup>4</sup> Biochemical genetic screening of newborns now can be efficiently extended to at least 20 disorders of amino acids, organic acids, and fatty acids.<sup>5</sup> To date, 24 states have commenced expanded newborn screening using tandem mass spectrometry, 4 have not yet implemented mandated programs, and 4 offer nonmandated expanded screening.<sup>6</sup>

This expansion of mandatory screening, however, has proceeded despite concerns that problems encountered in the early screening programs in the 1960s will be repeated.<sup>7,8</sup> These problems included "fragmented, uneducated and hurried decision-making"<sup>9</sup> and a lack of controlled studies to assess treatment strategies and parental response to the screening process.<sup>10,11</sup> Questions remain regarding the benefits of earlier treatment and the impact on families when a positive screening result occurs.<sup>12-14</sup>

Expanding newborn screening raises at least 2 major concerns inherent in any screening program. One of these is the likelihood of an increase in the number of false-positive results. *False-positive results* are defined as initial out-of-range screening results that do not signify a metabolic disorder on further evaluation of the child. Generally, these are not laboratory errors, but rather transient findings. Reports of alterations in parent-child relationships and significant parental anxiety, depression, and persistent misconceptions appeared after screening for phenylketonuria began in the 1960s and 1970s,<sup>15</sup> resulting in a "vulnerable child syndrome" in which parents remain anxious and overprotective.<sup>16</sup> A second concern is the misinterpretation of mild and perhaps benign biochemical abnormalities as serious disease, requiring preventive treatment. An example of this is mild hyperphenylalaninemia, which is now known to be benign, but during the early years of newborn screening it was thought to

represent the potential risk for mental retardation.<sup>17</sup>

Massachusetts expanded its newborn screening program for metabolic disorders on February 1, 1999, as a supplement to disorders for which screening was already mandated. Additional metabolic disorders included medium-chain acyl-coenzyme A (CoA) dehydrogenase deficiency (MCADD), which was added to the list of mandated disorders to be screened, and 19 metabolic disorders screened on a pilot basis.<sup>7,18</sup> On July 1, 2001, Maine also added disorders to their mandated program, but as of December 1, 2002, when this data set was closed, no other New England states had implemented expanded newborn screening programs.

This article summarizes initial results from a cohort of children with metabolic disorders identified from February 1, 1999, through June 1, 2002, and who were evaluated by December 1, 2002. Children identified by expanded newborn screening in Massachusetts and Maine were compared with those identified clinically from any New England state. To increase the number of children with positive expanded screens, a private newborn screening laboratory in Pennsylvania also contributed to the cohort. The New England Consortium of Metabolic Programs<sup>19</sup> facilitated recruitment and ensured uniformity in diagnostic confirmation methods. The consortium included the New England Newborn Screening Program, which provides expanded newborn screening for Massachusetts and Maine, and representatives from each of the metabolic centers in the region. One-year follow-up evaluations will be conducted as a second phase of this study.

## METHODS

### Enrollment and Study Procedures

Families of infants whose diagnosis of a metabolic disorder was prompted by expanded newborn screening by the New England Newborn Screening Program in Massachusetts and Maine or by the private screening laboratory in Pennsylvania and families of infants and

children diagnosed with the same set of disorders on the basis of clinical presentation in any New England state were eligible to participate in the study. The Pennsylvania laboratory, Pediatrx Inc (formerly known as NeoGen Screening Inc), began supplemental screening in 1994 and now provides screening to more than 99% of birthing hospitals in Pennsylvania. Annual birthrates are approximately 81 000 for Massachusetts, 13 000 for Maine, and 150 000 for Pennsylvania.

Newborn screening programs report out-of-range results to the primary care physician listed on the newborn screening form. If the child is considered only "possibly" affected, a request for submission of a repeat filter paper blood specimen for follow-up testing is made. Alternatively, a request may be made for immediate referral to a metabolic clinic at one of the academic medical centers in which a multidisciplinary team of experts provides confirmatory assessments and ongoing care to children with metabolic disorders. Children identified clinically with the metabolic disorders included in this study were followed up at the metabolic centers, although some were initially identified elsewhere.

For this study, the directors of the metabolic centers (not the screening programs) in New England or Pennsylvania sent recruitment letters inviting both mothers and fathers of children identified clinically or by screening to participate. The letters were sent to families between 5 and 30 months after diagnosis. Parents who did not return an "opt out" reply form were contacted by telephone. After written informed consent was obtained, medical and neurodevelopmental evaluations of the child and interviews with each parent were conducted, usually in the family's home.

In addition, mothers and fathers of infants who had a false-positive screen result for any of the 20 biochemical genetic disorders in the expanded newborn screening protocol were invited to participate in a telephone interview 6 months after the diagnosis of a meta-

bolic disorder was ruled out. In Massachusetts and Maine, this group included only families referred to a metabolic center. In Pennsylvania, this group included families sent recruitment letters by the screening program. The screening program sent out recruitment materials to all known cases of infants with a false-positive screen result in Pennsylvania. The comparison group for the false-positive cohort included parents of 6-month-old children with normal newborn screening results selected sequentially from the Commonwealth of Massachusetts Department of Public Health Birth Registry of Vital Records and Statistics. The birth registry only included the infant's date of birth, the mother's name, and the hospital of birth. No matching criteria were applied. Families were recruited by letter and followed up by a telephone call if the opt out form was not returned. The recruitment letter contained all elements of informed consent, and consent was implied by agreement to the telephone interview.

Exclusions included parents of children who died prior to enrollment and, for the newborns in the normal screened group, parents of newborns whose birth weight was less than 2500 g. The latter exclusion prevented recruiting parents of premature newborns who often have a transient abnormality on initial newborn screening.<sup>20</sup> Human studies approval for all aspects of the study was obtained annually from institutional review boards of the Children's Hospital Boston and the individual metabolic centers.

### Data Collection

**Children With Metabolic Disorders.** Infants and children diagnosed with a metabolic disorder received a standard medical examination. Medical records were obtained from hospitals, emergency departments, metabolic centers, and primary care physicians. Measures of child functioning included the Bayley Scales of Infant Development, second edition,<sup>21</sup> administered through age 3 years; the Stanford-Binet Intelligence Scale fourth edition,<sup>22</sup> adminis-

tered to children older than 3 years; and the Vineland Adaptive Behavior Scales,<sup>23</sup> based on parental report of the child's communication, self-help, socialization, and motor skills.

**Parents.** Parents of affected children and parents of children with false-positive or normal screening results were interviewed and completed the Parenting Stress Index (PSI), third edition, short form.<sup>24</sup> The parent interview consisted of questions requiring short answers or ratings on a 5-point scale that related to background information, socioeconomic status,<sup>25</sup> and social support.<sup>26</sup>

The PSI<sup>24</sup> is a 36-item questionnaire providing a total stress score and 3 scaled scores: parental distress, parent-child dysfunction, and difficult child.  $\alpha$ -Reliability coefficients were between .80 and .87 for the scaled scores and .91 for the total stress score. In addition, parents of children with metabolic disorders completed the Client Satisfaction Tool,<sup>27</sup> a 12-item measure in which parents rate their health care professionals in terms of support, information, decisional control, and professional competence. Internal consistency ( $\alpha$ ) was .96 when used as a measure of satisfaction.

### Data Analyses

Wilcoxon rank sum test was used to compare the dichotomous groups (identification by newborn screening vs clinical presentation and false-positive vs normal screening results) with regard to continuous variables. Two-tailed Fisher exact test was used when evaluating differences of dichotomous variables. Spearman correlation analyses were conducted to identify variables related to parental stress. Non-parametric procedures avoided problems related to nonnormal distributions. Power analyses suggested that with 35 newborns in each group (relevant for newborn screened vs clinical identification comparisons), there would be 80% power to detect a 20% difference at  $P < .05$ . With 80 newborns in each group (relevant for false-positive vs normal screening compar-

isons), there would be 80% power to detect a 9% difference at  $P < .05$ . Results on parental stress were analyzed separately for mothers and fathers. Analyses focused on associations between variables and assessment of the magnitude of differences between groups. Statistical packages from STATA version 6 (Stata Corp, College Station, Tex) were used.<sup>28</sup>

## RESULTS

### Newborns

The sample included 50 affected children identified through expanded newborn screening (28 from Massachusetts, 6 from Maine, and 16 from Pennsylvania) and 33 affected children identified clinically. In addition, 94 children found to have false-positive newborn screening results (18 from Massachusetts and 76 from Pennsylvania) and 81 unaffected children having normal newborn screening results (all from Massachusetts) were enrolled.

A total of 254 mothers and 153 fathers were interviewed. For 149 infants, both parents responded. The number of families who enrolled divided by the number of families contacted determined the participation rates: 82% in the newborn screened group; 97% in the clinically identified group; 75% in the false-positive group; and 63% in the normal-screened comparison group. Newborn screened children who were not enrolled had the same diagnoses as those enrolled, except that 2 disorders, suspected by elevated tyrosine and elevated glutaryl-carnitine levels, were not represented in the newborn screened group.

We excluded 43 families of children who were clinically identified from 2 metabolic centers that failed to obtain approval from their internal review board for the study, 10 children who were newborn screened, 202 with false-positive results, and 144 control families who could not be contacted by mail or telephone. Five additional infants who died within 5 days of birth, despite early identification through newborn screening, were not en-

rolled. Their deaths were attributed to complications of neonatal carnitine palmitoyltransferase II deficiency (1 child), long-chain hydroxyacyl-CoA dehydrogenase deficiency (2 children), arginase deficiency (1 child), and very long-chain acyl-CoA dehydrogenase deficiency (1 child).

The most frequent disorder among the newborn screened group was MCADD, with 20 cases, followed by very long-chain acyl-CoA dehydrogenase deficiency (TABLE 1). Among the clinically identified children, propi-

onic acidemia (PPA) was the most frequently diagnosed disorder with 6 cases, followed by MCADD (5 cases) and glutaric acidemia type II (4 cases). The children in the clinically identified group presented with symptoms of metabolic crises (vomiting, dehydration, hypoglycemia); none were identified solely on the basis of developmental delay, motor deficits, or mental retardation. In this group, 2 children died during the study: one at age 5 months with late infantile carnitine palmitoyltransferase II deficiency and the other at age

5 years with PPA. Two children with short-chain acyl-CoA dehydrogenase deficiency in the clinically identified group had been newborn screened, and they had a normal newborn screening result.

No significant differences were shown between the groups in background characteristics except that all parents in the normal-screened group were married, because the public registry of vital statistics only lists infants born to married couples (TABLE 2). The other groups included single-parent families and unmarried couples. As expected, the children in the clinically identified group were older at diagnosis than the children in the newborn screened group (median, 4 months vs 5 days;  $z=4.88$ ,  $P<.001$ ) and older at evaluation (median, 34 vs 9 months;  $z=5.45$ ,  $P<.001$ ). The children with normal newborn screening results were younger than the children with false-positive results (median, 6 vs 11 months;  $z=10.45$ ,  $P<.001$ ), a function of delays in differentiating false-positive from true-positive results.

### Early Identification of Metabolic Disorders Through Newborn Screening

**Effect on Medical Outcome.** Only 2 children in the newborn screened group diagnosed with MCADD and long-chain hydroxyacyl-CoA dehydrogenase deficiency required care in the neonatal intensive care unit prior to diagnosis compared with 7 children with MCADD (2 children), very long-

**Table 1.** Disorders and Numbers of Affected Children Represented Among Enrolled Newborns

	Newborn Screened Group (n = 50)	Clinically Identified Group (n = 33)
MCADD	20	5
SCADD	4 + 1 presumptive	2 + 1 presumptive
VLCADD	5 + 2 presumptive	2
LCHADD	2 + 1 presumptive	1
Fatty acid oxidation disorder, unclassified	1	0
Propionic acidemia	3	6
Methylmalonic acidemia	2	1
Arginosuccinic acidemia	1	1
3 MCC deficiency	3	0
Citrullinemia	2	0
Isovaleric aciduria	2	0
Methyl/butyryl CoA dehydrogenase deficiency	1	0
Glutaric acidemia type I	0	3
Glutaric acidemia type II	0	4
Tyrosinemia I	0	3
Arginase deficiency	0	2
Cobal C deficiency	0	1
Carnitine palmitoyltransferase II deficiency	0	1

Abbreviations: CoA, coenzyme A; LCHADD, long-chain hydroxyacyl-CoA dehydrogenase deficiency; MCADD, medium-chain acyl-CoA dehydrogenase deficiency; 3-MCC, 3-methylcrotonyl-CoA carboxylase; SCADD, short-chain acyl-CoA dehydrogenase deficiency; VLCADD, very long-chain acyl-CoA dehydrogenase deficiency.

**Table 2.** Demographic Information

	Newborn Screened Group (n = 50)	Clinically Identified Group (n = 33)	P Value*	False-Positive Group (n = 94)	Group With Normal Newborn Screening Results (n = 81)	P Value*
Married families, No. (%)†	37 (74)	28 (85)	.29	78 (83)	81 (100)	<.001
Primary language is English, No. (%)†	44 (88)	30 (91)	.74	88 (94)	77 (95)	.75
Low social position, No. (%)†	14 (28)	14 (42)	.24	34 (36)	7 (9)	<.001
Child age at diagnosis, median (range)‡	5 d (1-180)	4 mo (0.1 mo-5.9 y)	<.001			
Child age at evaluation, median (range)‡	9 mo (5-91)	34 mo (4-101)	<.001	11 mo (5-25)	6 mo (4-10)	<.001
Child first born, No. (%)†	20 (40)	14 (42)	>.99	29 (31)	31 (38)	.34
Female, No. (%)†	23 (46)	15 (46)	>.99	46 (49)	39 (48)	>.99
White race, No. (%)†	39 (78)	29 (88)	.38	76 (81)	72 (89)	.21

\*Newborn screened group was compared with clinically identified group and false-positive group was compared with group with normal newborn screening results.

†Two-tailed Fisher exact test. Low social position a score >3 on Hollingshead Redlich Scale.<sup>25</sup>

‡Wilcoxon rank-sum test.

chain acyl-CoA dehydrogenase deficiency (2 children), long-chain hydroxyacyl-CoA dehydrogenase deficiency (1 child), and PPA (2 children) in the clinically identified group (TABLE 3). Twenty-eight percent of the newborn screened children but 55% of the clinically identified children required hospitalization at least once within the first 6 months of life. Children in the newborn screened group were treated a median of 4 months sooner than the children in the clinically identified group. The children in

the newborn screened group required a median of 1 less day in hospital at each admission. Sixty percent fewer children in the newborn screened group experienced symptoms at the time of diagnosis or complications after diagnosis. Vomiting and hypoglycemia were the most frequent problems for children in both groups. Differences in medical treatment regimens were not significant between the groups, but the clinically identified group was at least 3 times more likely to require additional interventions or special ser-

vices, such as early intervention or home nursing care.

**Effect on Developmental Status.** The newborn screened group had a median developmental quotient 14 points higher on the Mental Development Index of the Bayley Scales of Infant Development ( $z=2.39$ ,  $P=.02$ ) and 29 points higher on the Motor Development Index ( $z=3.22$ ,  $P<.001$ ) than the clinically identified group (TABLE 4). One of 2 children with methylmalonic acidemia identified by newborn screening performed in the range of mental retardation. No other children in the newborn screened group functioned in the range of mental retardation. Eight clinically identified children (42%) with PPA, short-chain acyl-CoA dehydrogenase deficiency, glutaric acidemia type I, glutaric acidemia type II, arginase deficiency, and cobalamin C deficiency performed in the range of mental retardation. In addition, 14 children who were clinically identified and older than 3 years received the Stanford-Binet Intelligence test. They attained a median IQ of 87 (range, 35-116), with 6 children (43%) with PPA, glutaric acidemia type I, glutaric acidemia type II, or arginase deficiency who performed in the range of mental retardation.

As measured by the Vineland Adaptive Behavior Scale, significant deficits in communication, daily living skills, socialization, and motor skills were noted among almost half the children who were clinically identified, but none were noted in the children who were newborn screened (Table 4).

**Impact on Resource Use and Satisfaction With Health Care.** Fifty percent of parents of affected children rated their understanding of newborn screening as inadequate. A primary care physician (usually a pediatrician) was the initial informant about the abnormal newborn screening result in 54% ( $n=27$ ) of newborn screened cases. Other informants were a nurse practitioner in 28% ( $n=14$ ), a metabolic physician in 12% ( $n=6$ ), and a health care professional from the newborn nursery in 6% ( $n=3$ ) of cases. For the clinically identified cases, the physician from

**Table 3.** Medical Status of Children Identified by Newborn Screening Compared With Children Identified Clinically

	No. (%)		P Value*
	Newborn Screened Group (n = 50)	Clinically Identified Group (n = 33)	
Transferred to NICU	2 (4)	7 (21)	.03
Hospitalized in first 6 months of life	14 (28)	18 (55)	.02
Symptoms at diagnosis	11 (22)	29 (88)	<.001
Medical complications	10 (22)	21 (64)	<.001
Neurological complications	7 (14)	19 (58)	<.001
Receiving treatment			
Carnitine	23 (46)	14 (42)	.82
Specific formula	8 (16)	7 (21)	.57
No treatment	13 (26)	4 (12)	.17
Early intervention	5 (10)	11 (33)	.02
Gastrostomy tube	2 (4)	8 (24)	.01
Wheelchair	0	3 (9)	.06
Special services	10 (20)	24 (73)	<.001

Abbreviation: NICU, neonatal intensive care unit.

\*Two-tailed Fisher exact test.

**Table 4.** Developmental Status of Children Identified by Newborn Screening Compared With Children Identified Clinically\*

	Newborn Screened Group (n = 50)	Clinically Identified Group (n = 33)
Bayley Scales of Infant Development		
No.	48	19
Age at assessment, median (range), mo†	9 (5-29)	22 (4-35)
Mental development, median (range)†	106 (66-145)	92 (49-114)
Motor development, median (range)†	101 (70-123)	72 (49-108)
Score <71 on mental scale, No. (%)‡	1 (2)	8 (42)
Score <71 on motor scale, No. (%)‡	2 (4)	8 (42)
Vineland Adaptive Behavior Scale		
No.	48	33
Age at assessment, median (range), mo†	9 (5-29)	34 (4-100)
Composite score, median (range)†	107 (71-153)	85 (48-114)
Score <71, No. (%)‡	0	12 (36)

\* $P<.001$  for all comparisons.

†Wilcoxon rank-sum test.

‡Two-tailed Fisher exact test for dichotomous comparisons.

the metabolic center disclosed the diagnosis in 55% (n=18) of cases while the primary care physician provided this information in 33% (n=11) of cases. Approximately 60% of parents in each group correctly recalled the recurrence risk for future pregnancies of their child's metabolic disorder. Only 3 fathers and 2 mothers reported receiving services from a genetic counselor.

The children visited their metabolic centers a median of 4 times per year and their primary care physicians 6 to 7 times per year. Parents rated their health care professional positively, with median scores on the Client Satisfaction Tool greater than 56 (of a maximum positive rating of 60) for all groups. Parents who expressed dissatisfaction most often cited concerns about their primary care physician's unfamiliarity with their child's metabolic disorder. Parents of children identified by newborn screening expressed greater satisfaction with their social support network than parents of children identified clinically (median, 5 vs 4 on a scale of 1-5;  $z=2.04$ ,  $P=.04$ ). Median monthly out-of-pocket medical costs were \$20 for the newborn screened group and \$30 for the clinically identified group, with a range of \$0 to more than \$1000 per month in both groups. More than half the families had private health insurance and all had some kind of medical insurance. Twenty-four percent (n=8) of families whose children were identified clinically engaged in medicolegal proceedings while none of the families in the newborn screened group contacted a lawyer with regard to their child's medical care ( $P=.001$ ).

**Impact on the Family.** Mothers in the newborn screened group reported significantly lower overall stress on the PSI than mothers in the clinically identified group ( $z=3.38$ ,  $P<.001$ ) (TABLE 5). Only 1 mother (2%) in the newborn screened group, but 14 mothers (42%) in the clinically identified group, scored in the clinical range ( $>85$ ), indicating a need for services ( $P<.001$ ). The differences were most pronounced on the difficult child ( $z=4.12$ ,  $P<.001$ ) and parent-child dysfunction ( $z=3.74$ ,  $P<.001$ ) subscales.

**Table 5.** Impact on the Family: Median Scores on the Parental Stress Index\*

	Newborn Screened Group	Clinically Identified Group	P Value†
Total score (range, 36-180)			
Mothers	61 (38-91)	80 (38-138)	<.001
Fathers	62 (38-99)	65 (40-116)	.42
Parental distress (range, 12-60)			
Mothers	26 (13-47)	30 (12-52)	.06
Fathers	24 (12-47)	25 (14-41)	.65
Difficult child subscale (range, 12-60)			
Mothers	18 (12-36)	25 (14-56)	<.001
Fathers	21 (12-36)	24 (12-47)	.26
Parent-child dysfunction subscale (range, 12-60)			
Mothers	14 (12-26)	19 (12-41)	<.001
Fathers	14 (12-29)	18 (12-28)	.79

\*Higher scores indicate higher stress: 81 mothers (48 in the newborn screened group; 33 in the clinically identified group); 54 fathers (39 in the newborn screened group; 15 in the clinically identified group).

†Wilcoxon rank-sum test.

Spearman correlation analyses indicated that maternal stress increased as the child's level of functioning decreased ( $\rho=.46$ ,  $P<.001$ ) and as satisfaction with social support decreased ( $\rho=.36$ ,  $P<.001$ ). For mothers in the newborn screened group, those rating their understanding of newborn screening as low compared with those rating their understanding as adequate or high had higher levels of stress (median score, 52 vs 73;  $z=2.5$ ,  $P=.01$ ). Fathers in the newborn screened group did not score differently from fathers in the clinically identified group on the PSI (median score, 62 vs 65;  $z=.90$ ,  $P=.42$ ).

Mothers in the newborn screened group compared with mothers in the clinically identified group were less likely to report a negative effect on reproductive plans, although 53% preferred not to have more children compared with 70% of those in the clinically identified group. Among fathers, 56% in the clinically identified group and 51% in the newborn screened group preferred not to have more children. In the newborn screened group, 60% of mothers reported that they would accept prenatal screening for their child's disorder in the future while 75% of mothers in the clinically identified group indicated that they would do so. However, only 1 mother of a newborn screened child and 2 mothers in the clinically identified group reported an intention to terminate the pregnancy if the fetus was affected.

**Table 6.** Parental Response to False-Positive Results (Mothers and Fathers: n = 104)

Parent Report of Reasons for Repeat Screen:	No. (%)
Correct responses	57 (55)
Initial test result was abnormal	25 (24)
Test indicated metabolic disorder	18 (17)
First test inconclusive	14 (14)
Inaccurate responses	24 (23)
Not enough blood collected	17 (16)
First test had a mistake or was lost	5 (5)
Repeat screen is routine	2 (2)
Other	23 (22)
Cannot remember	17 (16)
Nothing specific	4 (4)
Did not know that repeat was done	2 (2)

### False-Positive Group

**Interactions With Health Care Professionals.** Parents of children with a false-positive result reported that the median age when a repeat screen was collected was 10 days (range, 2-120 days) and the median time from collection to learning the result was 7 days (range, 1-120 days). Of the 82 mothers and 22 fathers responding to this question, 55% (n=57) correctly identified the reason for a repeat screen (TABLE 6). Thirty-five percent (n=33) of families reported receiving no feedback about the repeat specimen. Twenty families (21%) were referred to a metabolic center after an initial false-positive newborn screening result. These parents were 2 1/2 times more likely to report the correct reason for a follow-up blood test (80% vs 30%), and all were told the result of the repeat test.

**Impact on Child Health.** Twenty-one percent ( $n=20$ ) of children in the false-positive group were hospitalized (usually after an emergency department visit) compared with 10% ( $n=8$ ) of children in the comparison group ( $P=.06$ ). The most frequent reasons for admission were similar: respiratory syncytial virus, pneumonia, eczema, and fever. Parents of children referred to a metabolic center did not worry more about their child's health or visit the emergency department, hospital, or primary care physician more often than parents whose children were not referred to a metabolic center.

**Impact on the Family.** Mothers in the false-positive group had scores on the PSI significantly higher than mothers in the normal screened comparison group (median score, 67 vs 54;  $z=4.25$ ,  $P<.001$ ). They also scored significantly higher on the parent-child dysfunction subscale (median score, 16 vs 13;  $z=5.30$ ,  $P<.001$ ). Mothers in the false-positive group whose children were referred to a metabolic center had lower scores on the parent-child dysfunction subscale compared with mothers whose children were not referred to a metabolic center (median score, 13.5 vs 16;  $z=2.47$ ,  $P=.01$ ). Likewise, mothers who received the information about the results of the repeat screen in person were significantly less stressed compared with mothers who received no notification of the results or received this information by telephone or letter (median score, 55 vs 67;  $z=2.45$ ,  $P=.02$ ). Stress levels were unrelated to whether or not the mothers were married or of lower socioeconomic status. Parental stress in fathers of children with false-positive newborn screening results was not higher than that in fathers of children with normal newborn screening results (median score, 68 vs 61;  $z=1.63$ ,  $P=.10$ ).

## COMMENT

These preliminary results indicate that children in this cohort with biochemical genetic disorders identified by newborn screening may experience fewer developmental and health problems and

function significantly better in diverse aspects of daily living than children identified clinically. This finding is expressed by fewer than half the number of children hospitalized, shorter hospital stays, 60% fewer medical problems, and scores on developmental tests 1 to 2 SDs higher in the newborn screened group compared with the clinically identified group. These positive outcomes corroborate cost-effectiveness projections on the value of earlier identification and treatment for metabolic disorders.<sup>29-31</sup> However, despite newborn screening identification, 5 children who were not enrolled in this study died shortly after birth and 2 children with short-chain acyl-CoA dehydrogenase deficiency were not identified. Furthermore, some children in the clinically identified group appear to be developing normally despite having experienced metabolic crises that led to their diagnoses. These findings need to be considered in the overall evaluation of the effectiveness of expanded newborn screening programs.

Expanded newborn screening extends the role of the primary care physician who is most often called on to inform parents of an abnormal screening result. While metabolic centers provide care related to the metabolic disorder, the primary care physician provides routine care and acute care for illnesses, in which the metabolic disorder needs to be considered. The newborn screened children saw the primary care physician almost twice as often as their metabolic specialist. Although parents generally expressed satisfaction with primary care physicians, some parents cited their unfamiliarity with the metabolic disorder as a source of dissatisfaction.

Newborn screening conferred benefits to parents. Parents of children who were newborn screened compared with parents of children who were clinically identified expressed lower levels of stress and greater satisfaction with their support network. They were less likely to consult a lawyer regarding health care concerns. Similar results were found in a retrospective study of parents of older

patients with metabolic disorders (median age, 9 years) in New England, suggesting that positive outcomes related to newborn screening persist.<sup>32,33</sup> On the other hand, false-positive findings in newborn screening generate anxiety in parents. Their children were twice as likely to have an emergency department visit or hospitalization than children in the comparison group. Other studies suggest that these results are related to persistent altered perceptions of the child's health.<sup>34</sup>

This study has a number of limitations. Follow-up was short. Long-term follow-up is needed to determine if children identified and treated on the basis of newborn screening continue to experience better health and development than children identified because of clinical symptoms. While treatments are available for all disorders included in expanded newborn screening, the long-term benefits of early identification and treatment have yet to be established. The age disparity between the newborn screened and clinically identified groups is a potential confounder. To address this limitation, an interim analysis was conducted on selected data from the next phase of the study: results from the 1-year follow-up evaluations of a subgroup of 22 newborn screened children (median age, 21 months; range, 15-22 months) were compared with results from the initial evaluations of a subgroup of 19 clinically identified children (median age, 22 months; range, 4-35 months). The median Bayley Mental Development Index was 17 points higher in the newborn screened group compared with the clinically identified group (99 vs 82;  $z=2.10$ ,  $P=.04$ ) and the Motor Development Index was 26 points higher (100 vs 74;  $z=3.87$ ,  $P<.001$ ). The median PSI score of mothers of children in the newborn screened group was 66 (range, 36-91) while that of mothers of children in the clinically identified group was 80 (range, 38-138) ( $z=1.06$ ,  $P=.29$ ).

In addition to differences in age, the diagnoses of the children identified by newborn screening vs by clinical iden-

tification are potential confounding variables. A disproportionate number of children in the newborn screened group had MCADD. When analyses were performed without children with MCADD and then with those with MCADD exclusively, results were similar to results from the larger sample in terms of developmental quotients, number of hospitalizations, and parental stress.

Delays in confirming results presented a challenge for the study. One newborn screened child with an unclassified fatty acid oxidation disorder is now, at 2 years of age, being evaluated for a mitochondrial disorder. The diagnoses of other children in the study also may be revised in the future.

Expanded newborn screening programs may be identifying children with benign or mild forms of the disorders, which may account for the results rather than earlier identification and treatment. Wilcken et al<sup>35</sup> reported that in the 3 years of expanded screening in Australia, 55 infants with metabolic disorders (excluding phenylketonuria) were identified. In the immediately preceding 3 years, only 32 cases of these metabolic disorders were clinically identified, suggesting that other affected children remained healthy or had died without a diagnosis. The former explanation is supported in our study by the discovery of healthy, older affected siblings. Eight affected siblings (7 with MCADD and 1 with 3-methylcrotonyl-CoA carboxylase [3-MCC] deficiency) were discovered subsequent to newborn screening identification of a younger sister or brother. Of these siblings, 4 with MCADD had clinical features of the disorder, including episodes of hypoglycemia and extreme lethargy, but the other 4 siblings were asymptomatic. At the time of evaluation, all 8 siblings were functioning within the average range, although 2 siblings with MCADD demonstrated language delay. The siblings with MCADD currently receive treatment (avoidance of fasting and a low-fat diet), but the child with 3-MCC deficiency remains untreated and healthy. More-

over, children with MCADD identified by newborn screening may have different MCADD genotypes from those associated with severe metabolic episodes and sudden death.<sup>36,37</sup> In our sample, only 4 of 18 children receiving genetic testing for MCADD in the newborn screened group were homozygous for the common severe A985G mutation, while all 4 of the clinically identified children tested were homozygous for this mutation. Possibly, children with MCADD identified by newborn screening have a higher frequency of mild forms of this disorder.<sup>37</sup> Longitudinal studies with the potential for identifying genetic variations and greater numbers of older affected siblings may further understanding of the natural history of these disorders.<sup>38,39</sup> Once the genotype-phenotype relationships are better described, performing a genotype for MCADD and other disorders may be appropriate follow-up for newborn screening.

## CONCLUSIONS

Despite its limitations, this study highlights some of the challenges to current newborn screening practices. It demonstrates a need for education about newborn screening for parents prior to the birth of their child. Education about these rare and complex metabolic disorders also is needed for primary care physicians and other health care professionals, especially since face-to-face discussions with these professionals appear to reduce parental stress. Genetic counselors, rarely consulted, also may provide valuable reproductive counseling and information. Basic concepts such as carrier status and the meaning of a false-positive finding would be helpful for parents of all children who have a positive screening result.

Despite expanded newborn screening's apparent positive impact on the health and well-being of infants with metabolic disorders and their families, questions remain. What level of parental stress related to false-positive identifications will be tolerated within our society? Will changes in how information is communicated to parents relieve this

stress? To what extent is improvement in outcome related to the types of disorders being identified by screening? Do the benefits of expanded newborn screening outweigh its long-term costs in terms of quality-of-life considerations and financial burden? Hopefully continued study will permit detailed analyses of these questions so that rational decision making will occur.

**Author Contributions:** Dr Waisbren had full access to all the data in this study and takes responsibility for the integrity of the data and the accuracy of the data analyses.

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**Role of Collaborator:** NeoGen Screening/Pediatrix did not participate in the design of the study. With the collaboration of Dr Naylor (previous owner of NeoGen), an employee of NeoGen sent out the recruitment packages and conducted the interviews. No one else from NeoGen was permitted to read the notes from the interviews. NeoGen was not directly involved in the analysis of the data. Dr Naylor and the employee of NeoGen reviewed the analyses and made suggestions regarding interpretation of the data. They were not directly involved in the preparation of the manuscript but reviewed the manuscript, made suggestions, and approved the final manuscript.

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