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Newborn Screening by Tandem Mass Spectrometry for Medium-Chain Acyl-CoA Dehydrogenase Deficiency: A Cost-Effectiveness Analysis

Laura N. Venditti, MSc*; Charles P. Venditti, MD, PhD*‡; Gerard T. Berry, MD‡‖; Paige B. Kaplan, MD‡; Edward M. Kaye, MD‡; Henry Glick, PhD§; and Charles A. Stanley, MD‖

ABSTRACT. *Objective.* **To determine whether newborn screening by tandem mass spectrometry (MS/MS) for medium-chain acyl-CoA dehydrogenase deficiency (MCADD) is cost-effective versus not screening and to define the contributions of disease, test, and population parameters on the decision.**

Methods. **A decision-analytic Markov model was designed to perform cost-effectiveness and cost-utility analyses measuring the discounted, incremental cost per life-year saved and per quality-adjusted life-year saved of newborn screening for MCADD compared with not screening. A hypothetical cohort of neonates made transitions among a set of health states that reflected clinical status, morbidity, and cost. Outcomes were estimated for time horizons of 20 and 70 years. Probabilities and costs were derived from a retrospective chart review of a 32-patient cohort treated over the past 30 years at the Children's Hospital of Philadelphia, clinical experience with MCADD patient management, patient-family interviews, cost surveys, state sources, and published studies. In addition to older patients who came to medical attention by symptomatic presentation, our patient group included 6 individuals whose MCADD had been diagnosed by supplemental newborn screening. Estimates of the expected net changes in costs and life expectancy for MCADD screening were used to compute the incremental cost-effectiveness ratios. Sensitivity analyses were performed on key input variables, and 95% confidence intervals (CIs) were computed through second-order Monte Carlo simulations.**

Results. **In our base-case analysis over the first 20 years of life, the cost of newborn screening for MCADD was approximately $11 000 (2001 US dollars; 95% CI: <$0–$33 800) per life-year saved, or $5600 (95% CI: <$0–$17 100) per quality-adjusted life-year saved compared with not screening. Over a 70-year horizon, the respective ratios were approximately $300 (95% CI: <$0–$13 000) and $100 (95% CI: <$0–$6900). The results were robust when tested over plausible ranges for diagnostic test sensitivity and specificity, MCADD prevalence, asymptomatic rate, and screening cost.**

Conclusions. **Simulation modeling indicates that newborn screening for MCADD reduces morbidity and mortality at an incremental cost below the range for accepted health care interventions. At the 70-year horizon, the model predicts that almost all of the additional costs of screening would be offset by avoided sequelae.** *Pediatrics* **2003;112:1005–1015;** ***cost-utility, cost-effectiveness, newborn screening, inborn errors of metabolism, MCADD.***

ABBREVIATIONS. IEM, inborn error of metabolism; MS/MS, tandem mass spectrometry; MCADD, medium-chain acyl-CoA dehydrogenase deficiency; PKU, phenylketonuria; QALY, quality-adjusted life-year; USD, US dollars; CI, confidence interval.

Inborn errors of metabolism (IEMs) represent a heterogeneous group of genetic disorders that collectively are an important cause of morbidity and mortality in childhood.[1–3] Newborn screening has previously been available for only a few of these conditions. However, the application of newer methods for metabolite analysis in infant blood spots has substantially expanded the scope of disease detection and has led many states and countries to reassess which IEMs to include as part of the "routine" newborn screening panel.[4,5]

Tandem mass spectrometry (MS/MS) has been advanced as a tool in population-based screening for

From the *Department of Genetics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; ‡Division of Human Genetics and Molecular Biology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; §Department of General Internal Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; and ‖Division of Endocrinology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania.

Ms Venditti and Dr Venditti contributed equally to this work.

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Address correspondence to Charles P. Venditti, MD, PhD, Genetic Disease Research Branch, National Human Genome Research Institute, National Institutes of Health, Bldg 49 Rm 4A56A, Bethesda, MD 20892-4472. E-mail: venditti@mail.nih.gov

IEMs.[6,7] This method assays a single blood sample for the presence and relative concentrations of acylcarnitine esters and several amino acids. It is rapid, highly sensitive and specific, and amenable to automation and can be adapted to the Guthrie collection protocols in use by most screening programs.[8–12]

One fatty acid oxidation disorder that can be detected with a high degree of sensitivity and specificity using this method is medium-chain acyl-CoA dehydrogenase deficiency (MCADD).[13,14] MCADD seems to be as common as phenylketonuria (PKU), for which universal screening is mandated in every state and occurs at an incidence of 1 in 11 000 to 1 in 15 000 live births.[15–18] Because fatty acids are an important source of energy during fasting, infants and young children with MCADD are prone to metabolic crises and death when they are acutely unable to match caloric intake with their needs.[19] Decompensation may occur during the stress of intercurrent infection or with prolonged fasting.[20] It has been reported that between 19% and 25% of patients with undiagnosed MCADD die during their first episode of metabolic decompensation[21,22] and that those who survive an initial crisis experience substantial morbidity.[21,22] Several studies have also retrospectively documented MCADD in infants who had previously received a diagnosis of sudden infant death syndrome.[23–25]

Unlike some other metabolic diseases, the complications of MCADD are preventable. If infants are detected before a life-threatening episode, then they can be treated by instructing the parents to avoid fasting stress and provide calories through oral feedings every 4 to 6 hours in the first years of life. During periods of illness, constant useable carbohydrate calories are administered to prevent extensive lipolysis, and if oral intake fails, then medical triage for intravenous glucose is required. Because MCADD is relatively common, detectable with a high degree of certainty through MS/MS, and easily treated and can be associated with excellent outcomes if managed expectantly, it represents a good candidate disease to identify by newborn screening.[26]

The advent of MS/MS-based newborn screening has precipitated a critical reappraisal of disorders mandated by states for identification and treatment. According to the National Newborn Screening and Genetics Resource Center, as of December 2002, 15 states have mandated screening for MCADD and 8 are conducting pilot programs to assess the feasibility of MS/MS screening (go to http://genes-r-us.uthscsa.edu/resources/newborn/screenstatus.htm). In addition, a number of states that use MS/MS for newborn screening do not mandate screening for MCADD (go to http://genes-r-us.uthscsa.edu/resources/newborn/screenstatus.htm and http://www.savebabies.org). Because MS/MS screening may become a routine method for population-based screening for aminoacidopathies such as PKU, an important and unresolved question is the effectiveness and cost-effectiveness of using this technology to diagnosis infants who have other IEMs such as MCADD. As a starting point for a more comprehensive analysis of the application of MS/MS to routine newborn screening and more specifically to the detection of MCADD, we used Markov and probabilistic methods to construct a simulation model to study the cost-effectiveness and cost-utility of population screening for MCADD. Data for the model were derived from a review of a large, single-center patient cohort that included symptomatic and MS/MS-diagnosed patients and from a review of the literature. Simulation and sensitivity analyses have allowed the definition of critical parameters for the screening decision and the statistical framework for their interpretation.

METHODS

Model

We constructed a decision-analytic Markov model[27,28] to evaluate clinical outcomes for a hypothetical cohort of neonates who did or did not undergo universal screening for MCADD in the newborn period. We populated this model with primary data and simulated the clinical course of the cohort from birth through ages 20 and 70 years. The subjects in the hypothetical cohort were assumed to make annual transitions among a set of health states that reflected clinical status and morbidity. Each health state was associated with an annual cost, an annual utility value, and a set of probabilities of subsequent events. The time spent in each state was used to calculate life expectancy, quality-adjusted life-years (QALYs), and costs.[28] We adopted a societal perspective for our model and followed the recommendations of the Panel on Cost-Effectiveness in Health and Medicine.[29,30]

Strategies

We modeled 2 competing strategies (Fig 1). In the first strategy (Fig 1A), neonates do not undergo universal screening. Infants either have or do not have the disorder. Unscreened infants without the disorder are unaffected and treated as normal infants. Unscreened infants with the disorder are in 1 of 4 health states: asymptomatic MCADD, undiagnosed MCADD, diagnosed MCADD, or death. Asymptomatic MCADD represents individuals who have the disorder but whose health will never be affected by it. Undiagnosed MCADD represents those who have the disorder and are at risk for its adverse outcomes and either have yet to experience these outcomes or have experienced them but have not received a diagnosis of MCADD. Diagnosed MCADD represents those who have had an adverse health outcome that has led to the detection of their disorder. Those in the death state have died from either MCADD-related or natural/other causes.

The second strategy represents universal screening (Fig 1B). In this strategy, infants can test positive or negative. Those who test positive may have the disease (true positive) or not (false positive). We assume that 100% of those who test positive will receive a subspecialist evaluation. Those who test negative also may have the disease (false negative) or not (true negative). Infants with true positive tests are in either the MCADD or the death health state. Infants in the MCADD state are treated according to their diagnosis. Some of these infants may actually be asymptomatic through their lifetime and not require any intervention had they not been identified at birth; however, in our model, they engage in clinical encounters, accrue costs, and incur decrements in QALYs as a result of their diagnosis. Infants with true negative tests are considered unaffected and thus are treated like normal infants. Infants with initial false-positive tests incur costs in the short term as a result of the misdiagnosis (and lose QALYs in a sensitivity analysis) but in the long term are also considered unaffected because all infants with positive tests undergo confirmatory testing before the definitive diagnosis is rendered. Finally, infants with false-negative test results have outcomes that are similar to the unscreened infants with disease (Fig 1A).

Clinical Data

The data used in the model are shown in Table 1. Sources of data included retrospective chart review, patient/family interviews, and expert clinical opinion. The authors (C.P.V., G.T.B.,

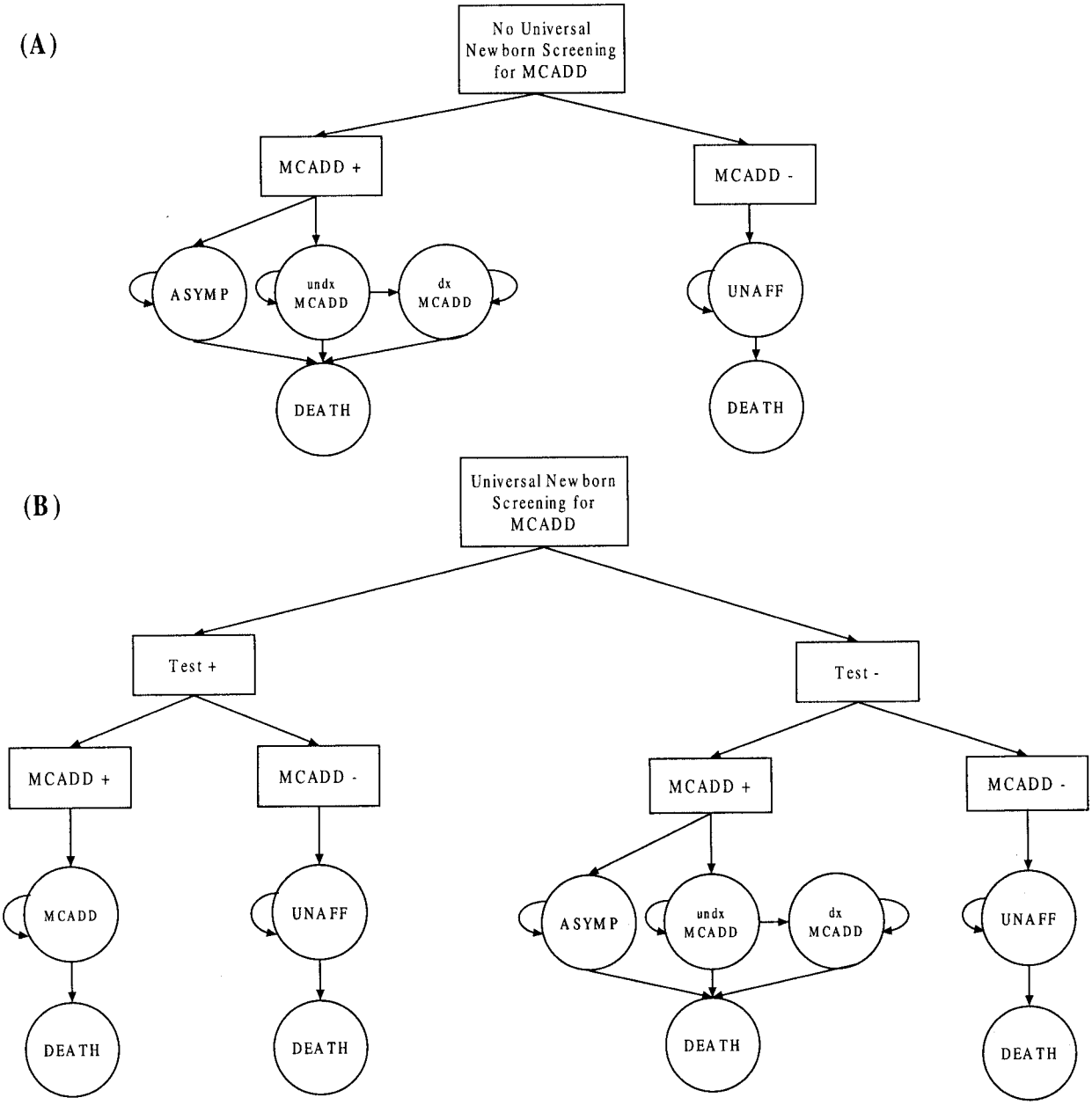

Fig 1. Markov model design.

P.B.K., E.M.K., and C.A.S.) have extensive experience treating individuals with genetic metabolic diseases, especially MCADD.[19,20] Secondary data from published reports, when available, were used to verify our estimates.[21]

Unscreened MCADD

The natural history of the unscreened MCADD state is not fully defined. A proportion of patients are biochemically/enzymatically affected but do not have symptoms and/or may not have been recognized to have symptoms. Although the proportion of patients with asymptomatic MCADD has not been measured prospectively, some studies have reported an approximation of 12%,[21,31] although this is uncertain.[22,32] Because this factor may be critical in the screening decision, we included the asymptomatic MCADD state in our unscreened decision arm and used a point estimate of 25% for the proportion asymptomatic.

For unscreened infants with symptomatic MCADD, we projected the clinical course during the first 20 years of life by use of primary data derived from retrospective chart review. The 32 subjects whose charts were reviewed received metabolic care over the past 30 years at the Children's Hospital of Philadelphia; 6 patients were diagnosed by supplemental newborn screening. On the basis of secondary reports,[21] we estimated that 10% of infants who survive until diagnosis will experience severe neurologic damage and significant disability, such as cerebral palsy. For projecting the clinical course beyond 20 years of age, the data were supplemented by expert opinion.

Screened MCADD

The clinical course of infants who have true positive screens for MCADD is also not fully understood. We used primary data, derived from retrospective chart review, to construct a database similar to that for the unscreened patients with MCADD and derived estimates of event probabilities and cost estimates for the first 10 years of patients' lives. Expert opinion was used to estimate resource use beyond the 10th year of life.

On the basis of these data, we assumed that all children who test positive for MCADD have their diagnoses confirmed during an initial outpatient specialty visit. The workup during this visit was assumed to include a repeat acylcarnitine profile, carnitine quantitation, urine organic acid analysis, and mutation studies if they had not been performed before the visit. We assumed that all

TABLE 1. Selected Model Variables

Variable	Base-Case Value	Analysis Range	Source
MCADD Prevalence	1/15 000	1/10 000–1/50 000	18
MS/MS screening test performance			
Sensitivity	1.0	0.95–1	18
Specificity	0.999996774	0.995–1	18, 26
Natural history			
% Asymptomatic MCADD	0.25	0–0.9	21,31
Risk of coma—unscreened MCADD (undiagnosed)*†	0.64	0.5–0.8	Primary data
Risk of coma—screened MCADD‡	0.0	0–0.1	Primary data
Mortality risks			
Screened MCADD	National average	1000% of base case	35
Unscreened MCADD (undiagnosed)*	0.09	0.04–0.15	Primary data
Unscreened MCADD (diagnosed)§	National average	1000% of base case	35
Health utilities			
Screened MCADD	0.99	0–1	Expert opinion
Disutility from false-positive screen	0.0	−0.03–0	39, 45
Unscreened MCADD (undiagnosed)	0.65	0–1	Expert opinion, 41–44
Unscreened MCADD (diagnosed)	0.80	0–1	Expert opinion, 41–44
Asymptomatic MCADD	1.0	—	Expert opinion
Costs (2001 USD)			
Screening and follow-up	$4	$1–$20	State screening programs (PA, WI, MA/ME), Neo Gen Screening, Inc
Confirmatory evaluation for positive screen	$2120	$0–$5000	Primary data, expert opinion
Carnitine for screened MCADD (annual)	$0	$0–$1000	Primary data
Care for severely affected (annual)	$1914	$0–$4000	36
Annual time discount rate	0.03	0–0.07	29

* First year probability only.
† Refers to the probability that a child with unscreened, symptomatic MCADD experiences a coma during a hospitalization or an emergency department visit (see Fig 1A, MCADD+, "undx MCADD").
‡ Refers to the probability that a child with screened MCADD (thus, diagnosed) experiences a coma during a hospitalization or an emergency department visit (see Fig 1B, Test+, MCADD+, "MCADD").
§ Refers to the annual probability of death for a child with unscreened (symptomatically) diagnosed MCADD (see Fig 1A, MCADD+, "dx MCADD").

newborn screen-positive patient-families would receive extensive education and emergency department protocols, special diets would not be prescribed, supplemental carnitine would not be administered in the well state, and parents would not be instructed to use glucometers. We examined all of these parameters in sensitivity analyses. Finally, we assumed that MCADD-positive patients would utilize the emergency department for intravenous glucose during times of intercurrent illness with clinical event probabilities similar to our cohort but otherwise were well and experienced no episodes or sequelae of severe metabolic decompensation.

Screening Tests

Because Neo Gen Screening Inc is one of the largest providers of MS/MS newborn screening tests, we used values for disease prevalence and test sensitivity and specificity derived from their prospective neonatal screening experience as of January 2001. The proportion of infants with MCADD in their screened population of 930 078 neonates was approximately 1 in 15 000.[18] This baseline estimate is in the range that others have described.[15–18,26] Because Neo Gen Screening Inc has reported no false-negative results, in the base-case analysis we assumed a sensitivity of 1.0 and assumed a specificity of 0.999996774.[18,26] We examined ranges for these values in sensitivity analyses.

Costs

We modeled the costs of screening and of treatment for MCADD and its sequelae. All costs were expressed in 2001 US dollars (USD).

Screening

Under the universal screening strategy, every newborn incurs a screening cost of $4.00. This estimate represents the incremental expense of adding MCADD to a preexisting MS/MS-based screening program and includes the cost of metabolite analysis (including repeated testing on the same bloodspot and any repeated tests as a result of inadequate initial samples) as well as the cost of follow-up. Follow-up costs were defined as the administrative and miscellaneous expenses required to identify the patient through contact with the designated physician; coordinate an initial confirmatory clinic visit; educate the parents; and longitudinally manage patient care through a network of genetic counselors, social workers, and nurses. Although this cost will likely vary between states, our estimate is conservative given the experience of other screening programs. For example, in 2000, Wisconsin added screening for 14 fatty acid oxidation and organic acid disorders including MCADD to its newborn screening panel at a cost of $7 per test ($4 for testing, $3 for treatment); their $4 testing cost reflects the incremental cost of starting and operating MS/MS technology (go to http://www.slh.wisc.edu/newborn/newsletters/2000/news0300.shtml).[33]

Our sensitivity analysis on the cost of MCADD screening addresses both variations from our base-case estimate as well as the likely results for state programs that have not yet implemented MS/MS. The $1 to $20 range used amply covers the addition of start-up and operating incremental costs of MS/MS technology as estimated by Wisconsin ($4) and by the American College of Medical Genetics/American Society of Human Genetics Test and Technology Transfer Committee Working Group ($10).[34]

As previously indicated, all children who test positive for MCADD have an initial confirmatory clinic visit. The cost of the visit and confirmatory testing was estimated by use of laboratory and outpatient physician fee data from the Children's Hospital of Philadelphia. The opportunity cost of 4 hours' time for both parents (using average age and sex-specific federal wage rates[35]) and related non-health care costs (eg, transportation costs) were incorporated into this estimate.

Treatment

Our analysis considered all direct medical costs incurred in the different health states, regardless of source of payments. Medical costs included those for inpatient, outpatient, and emergency department visits as well as physician fees. Nonmedical costs such as transportation and lost parental time from work were also included; unrelated future health care costs were not.

Medical

To estimate treatment costs for both strategies, we first used primary data from our 32-patient cohort and from patient-family interviews to estimate the annual risks and averages for inpatient stays, emergency department visits, and outpatient visits. Second, using the same data, we calculated the probabilities for specific clinical events related to hospitalizations (eg, coma) and the average accompanying resource use based on Children's Hospital of Philadelphia patient management. We also used these data to estimate the average resource use per outpatient and emergency department visit and the cost of these visits. We used secondary data sources to 1) validate the primary data; 2) estimate the risks for seizures and respiratory and cardiac arrest[21]; and 3) estimate the cost of long-term medical care, special education, and developmental services costs associated with severe neurologic damage and significant disability such as cerebral palsy, which can occur among children with symptomatic, undiagnosed MCADD.[21,36]

We calculated the average resource use (services, labs, tests, supplies, facility fees, and medications) per average inpatient stay, emergency department visit, and outpatient visit and estimated an average yearly medical charge for each health state in the model. To transform charges into best estimates of costs, we adjusted hospital charges by use of the cost-to-charge ratio from Children's Hospital of Philadelphia and adjusted professional fees by use of the average collection ratio.

Nonmedical

The cost for time in treatment incorporated parental cost estimates while the child was a minor and patient cost estimates after the child became an adult. Time and transportation cost estimates per hospital admission, emergency department visit, and outpatient visit were based on patient-family interviews, expert opinion, and cost surveys that were distributed via the Internet to affected patients and families in the Fatty Acid Oxidation Support Group (http://www.fodsupport.org) and Save Infants Through Screening (http://www.savebabies.org). We received responses to the latter survey from 32 families (there was no overlap between these respondents and the 32 children whose charts were reviewed). Data from these surveys confirmed the transportation and copayment values that we obtained from our primary data collection.

Average treatment time included travel, wait, and care time and depended on clinical encounter and decision arm (eg, we used 4 hours for either 1 parent or the patient per outpatient visit in both decision arms). We applied average age- and sex-specific hourly wage rates[35] to estimated time and added related transportation costs to determine total nonmedical costs. Although our study viewpoint was from the societal perspective, we did not include incremental caregiver time other than that for accompanying a child when consuming medical services, as any additional caregiver time was both uncertain and difficult to estimate with retrospective data because of recall bias.

Effectiveness

The sum of the annual cycles spent in all states other than death represented average life expectancy of members of the cohort. For infants who do not have MCADD, probabilities of death were derived from published age- and sex-specific annual mortality data.[35] For infants with unscreened MCADD, mortality rates were derived from primary data. On the basis of published reports, primary data, and expert opinion, we did not increase the mortality risk for patients with diagnosed MCADD in either decision arm for the base-case.[16,18,26]

Utility values reflect the life quality of the health state and allow morbidity and mortality improvements to be combined into a single weighted measure, QALYs saved.[37] These values generally range between 0 (death) and 1 (perfect health).[38] Although it may be possible to elicit community preferences for the health states associated with MCADD, the task is complicated by the combination and severity of symptoms and that the disease mainly affects infants and small children. Given the inherent difficulty in determining exact QALY weights and lack of existing studies in this particular area, we elected to compute quality-of-life weights by applying published utilities to the distribution of MCADD's outcomes[21] and explore the sensitivity of results to these weights.

We assumed that the utility for the unaffected state was 1.0. We assumed that the utility of the screened MCADD health state was 0.99. The 0.01 diminution accounts for disutility from expectant treatment anxiety[39] and reflects the absence of long-term morbidity that expectantly treated children experience (primary data).[21,26,32] We assumed that the utility for those who have been symptomatically diagnosed would be lower than that for those identified by screening.[4,16,21,31] To estimate this lower utility, we first identified published quality weights for health scenarios similar to those experienced by patients with symptomatically diagnosed MCADD before and after diagnosis.[40–44] We then calculated the utility as a weighted average by multiplying reported quality weights by the symptom and outcome distribution reported by Iafolla et al.[21] Our estimate for unscreened, symptomatic subjects postdiagnosis was 0.8. For infants with undiagnosed MCADD, we computed a utility estimate of 0.65, reflecting a more severe state than the former, with frequent and severe episodes of metabolic decompensation of unknown origin, manifested by coma, seizures, and cardiac and respiratory distress/arrest. We used the same utility values for the duration of the model's projection.

We did not account for the potentially substantial parental anxiety associated with symptomatic MCADD (eg, from witnessing a child in a severely compromised and undiagnosed health state, marked by episodes of seizures and coma; from witnessing and caring for a child who died or experienced significant morbidity as a consequence of that health state) or with false-positive screening reports because we did not include utilities for caregivers in our analysis. However, we accounted for anxiety as a result of false-positive screening reports in sensitivity analysis. Because there have been no studies that have measured disutility in the setting of false-positive testing for metabolic disease, we used a disutility estimate based on a review of cost-utility assessments in oncology.[39] This disutility estimate reflects the anxiety experienced for 3 months after a false-positive report and before the ultimate diagnosis is obtained. We estimated that it would range between −0.01 and −0.03 (annualized), which was based on the utilities for a false-positive breast cancer screen followed by a benign breast biopsy[39] and an indeterminate lung cancer diagnosis without underlying cancer, respectively.[39,45]

Analysis

We determined discounted total costs, years of life, and QALYs for both strategies as well as incremental ratios of discounted cost per year of life saved and discounted cost per QALY saved for 20- and 70-year time horizons. The cost-effectiveness ratios were calculated under the assumption that an MS/MS-based screening system was already in place for newborn screening (ie, only the variable costs of adding screening for MCADD are included in the analysis); we addressed those settings where it is not in place in sensitivity analysis. These ratios represent the incremental cost of gaining a single year of life or a single QALY if a universal screening strategy were implemented. We estimated 95% confidence intervals (CIs) for these ratios by use of second-order Monte-Carlo simulation.[46] Future costs and effects were discounted at 3% per annum. We also report the number of cases identified, the number of false-positive cases, the positive predictive value, the ratio of false-positive to true-positive cases, the total cost per true case detected, and the incremental cost per true case detected.

We performed extensive sensitivity analyses to determine the validity of our conclusions about the cost-effectiveness of universal screening to variations in a number of our assumptions.[38] Robustness was judged by whether changes in the assumptions led the resulting ratios to shift from one side to the other of a specific cost-effectiveness ratio. Although we have not presupposed a specific ratio, we have assumed possible acceptability ratio thresholds of $50 000/QALY or $100 000/QALY, ratios at which health care interventions have generally been considered to be cost-effective.[47,48]

First, we undertook a threshold analysis to identify values of

the variables that would cause the ratio to shift from one side to the other of $50 000/QALY and $100 000/QALY. Variables assessed included the MCADD prevalence (range: 1/10 000–1/50 000); the proportion of MCADD patients that are asymptomatic (0%–90%), test sensitivity (0.95–1.0) and specificity (0.995–1.0); mortality risk (1000% of national average mortality probabilities); utilities for screened MCADD, unscreened and undiagnosed MCADD, and unscreened and diagnosed MCADD (each ranging between 0 and 1); the cost for the screening test ($1–$20); the cost for the confirmatory evaluation ($0–$5000); the cost for carnitine supplementation (not included in our base-case analysis; $1000 per year); the cost for care for those who are severely affected by MCADD ($0–$4000 per year); the discount rate (0%–7% per annum); and the 3-month disutility from a false-positive screen (not included in our base-case analysis; 0 to −0.03 annualized).

Second, because of the relevance and importance of the cost of the test and proportion of patients who are asymptomatic, we provided detailed information about how the cost-effectiveness of screening is affected by our assumptions about these variables. Finally, we performed 2-way sensitivity analyses that simultaneously evaluated 1) the impact of changes in MCADD prevalence and the cost of the universal screen and 2) the sensitivity and specificity of the screening test. Modeling and analyses were performed with DATA 4.0 software (TreeAge Software, Inc, Williamstown, MA) and Statistical Analysis Software version 8.2 (SAS Institute, Cary, NC).

RESULTS

Base-Case

Projected discounted costs, effectiveness, and cost-effectiveness results for 20- and 70-year time horizons are shown in Table 2. Results for the entire 2001 US cohort of neonates as well as for the average neonate are presented.

In the 20 years of follow-up after birth, our model predicted that screening for MCADD yields a gain of 990 QALYs (501 life-years) at an additional cost of approximately $5.5 million and detects 269 true cases of MCADD from the >4 million neonates initially screened. The average neonate who undergoes universal screening was projected to live 14.343873 discounted QALYs (14.343883 discounted years of life)

TABLE 2. Base-Case Cost-Effectiveness and Projected Outcome Measures for the 2001 US Newborn Cohort*

Variables	20-Year Horizon	70-Year Horizon
Model projections		
Total cost		
Do not screen	$13 485 520	$19 704 478
Screen	$19 009 981	$19 977 994
Difference	$5 524 461	$273 516
Total effectiveness (LYs)		
Do not screen	57 950 522	113 420 733
Screen	57 951 023	113 421 755
Difference	501	1022
Total effectiveness (QALYs)		
Do not screen	57 949 993	113 419 751
Screen	57 950 983	113 421 678
Difference	990	1927
Average cost per neonate		
Do not screen	$3.3379	$4.8772
Screen	$4.7053	$4.9449
Difference	$1.3674	$0.0677
Average effectiveness per neonate (LYs)		
Do not screen	14.343759	28.073598
Screen	14.343883	28.073851
Difference	0.000124	0.000253
Average effectiveness per neonate (QALYs)		
Do not screen	14.343628	28.073355
Screen	14.343873	28.073832
Difference	0.000245	0.000477
Cost-effectiveness		
Incremental cost-effectiveness ratios†‡		
Cost/LY (95% CI)	$11 000 (N-$33 800)	$300 (N-$13 000)
Cost/QALY (95% CI)	$5600 (N-$17 100)	$100 (N-$6900)
Other outcome measures		
No. of MCADD cases identified by screening		282
No. of false-positive cases		13
No. of true-positive cases		269
No. of true-positive cases, symptomatic		202
No. of true-positive cases, asymptomatic		67
Ratio of false positive/true positive		0.0484
Positive predictive value		0.9538
Cost per true case detected (over 20 y)		$70 600
Δ Cost per additional true case detected (over 20 y)		$54 600
Cost per true case detected (over 70 y)		$74 200
Δ Cost per additional true case detected (over 70 y)		$4100

LY indicates life-year; N, negative ratio.

* Cohort includes 4,040,121 infants; 2001 USD LY, and QALYs were discounted at 3%.

† The incremental cost-effectiveness ratio is the incremental costs over incremental life-years or QALYs, rounded to the nearest $100.

‡ Negative ratio was calculated for lower CI because cost to screen was less than cost not to screen.

of the 14.877475 discounted years that would potentially be available if there were no death or disability. The average neonate who does not undergo screening was projected to live 14.343628 discounted QALYs (14.343759 discounted years of life). Thus, we project that universal screening would add 0.000245 QALYs (0.000124 years of life) to a child's life. When follow-up was extended through 70 years after birth, these values approximately doubled.

During 20 years of follow-up, universal screening would add $1.37 to the discounted total cost of caring for children with an incremental cost of $5600 per QALY (95% CI: <$0–$17 100). When this was projected for 70 years, nearly all of the additional costs of screening would be offset by avoided sequelae; universal screening would add $0.07 to the total costs with an incremental cost of $100 per QALY (95% CI: <$0–$6900). The negative lower limit of the CI reflects our model's projection that the universal screening strategy may provide both lower costs and greater effectiveness than the alternative (ie, for the lower limit, screening "dominates" the alternative).[29] Although the ratios of cost per year of life saved were projected to be 2 to 3 times higher than ratios of the cost per QALY, all of the point estimates remained well below a value of $50 000 per year of life saved as did the upper limits of the 95% CIs for the 20- and 70-year projections.

Other outcomes measures presented for the 2001 US cohort of newborns include the number of cases identified, the number of false-positive cases, total cost per case, and the incremental cost per additional actual case detected. In the base-case, the projected positive predictive value is 0.9538, with a false-positive to true-positive ratio of 0.0484. Screening identifies approximately 282 cases, including 13 false positives. Over the 70-year horizon, the total cost per true case detected is $74 200 and the incremental cost per additional true case identified is approximately $4100.

Sensitivity Analysis

In 1-way threshold analyses for the 20-year horizon, results were not sensitive to wide ranges (Table 1) of most variables, including MCADD prevalence, test sensitivity and specificity, mortality risks for diagnosed MCADD, and the discount rate. In most cases, the ratio remained <$10 000 per QALY. Among the other variables, the $50 000 threshold was exceeded if the utility weight for the screened MCADD state (true positive) was valued at ≤0.76, if the asymptomatic rate was 76% or greater (Fig 2), or if the screening test cost exceeded $14.90 (Fig 3). The $100 000 threshold was exceeded only if the utility weight for the screened MCADD state (true positive) was valued at ≤0.75 or if the asymptomatic rate was 86% or greater. Even with the screening cost test at $20, the $100 000 threshold was not reached (Fig 3). These results suggest that even if we had included start-up and operating costs in the base-case, screening for MCADD would have had acceptable cost-effectiveness ratios. Disutility considerations for anxiety induced by false-positive screening reports did not significantly influence the model results even at the lower estimate tested (−0.03 annualized).

Figure 4 depicts the results of the 2-way sensitivity analyses that simultaneously evaluated the impact of changes in the MCADD prevalence and the cost of the universal screen. Each line represents cost per QALY results by screening cost, for a fixed MCADD frequency over a 20- or 70-year horizon. The $50 000 threshold was never exceeded when the MCADD prevalence was 1 in 10 000 or when it was 1 in 20 000 and costs and outcomes were projected for 70 years. Over the shorter time horizon, however, the $50 000 threshold was exceeded when the screening test cost was >$11.20 and the MCADD prevalence was 1 in 20 000. When the disease frequency was 1 in 50 000, the ratio was more sensitive to test cost and exceeded the $50 000 threshold for the 20-year horizon when

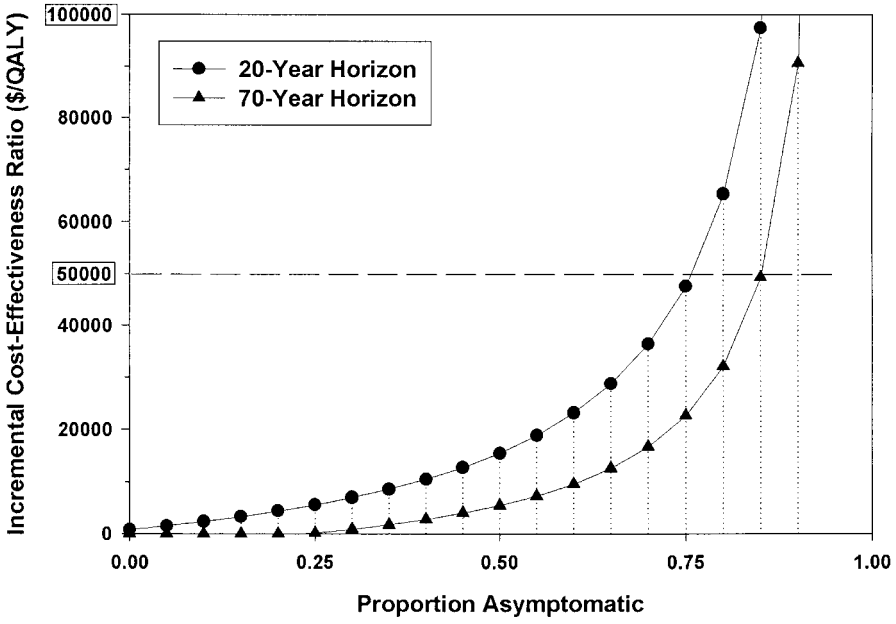

Fig 2. Base-case cost-effectiveness by proportion asymptomatic.

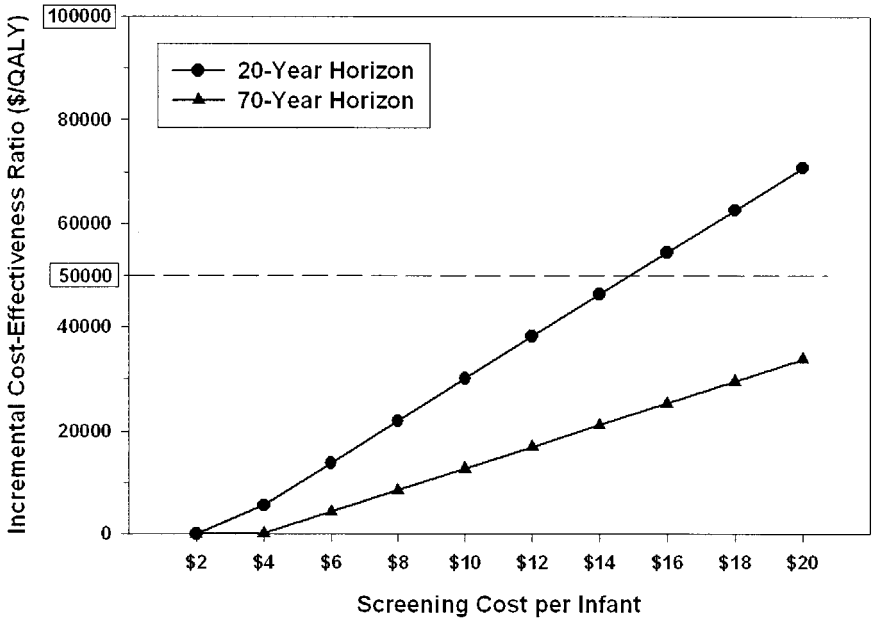

Fig 3. Base-case cost-effectiveness by screening cost (MCADD prevalence: 1 in 15 000).

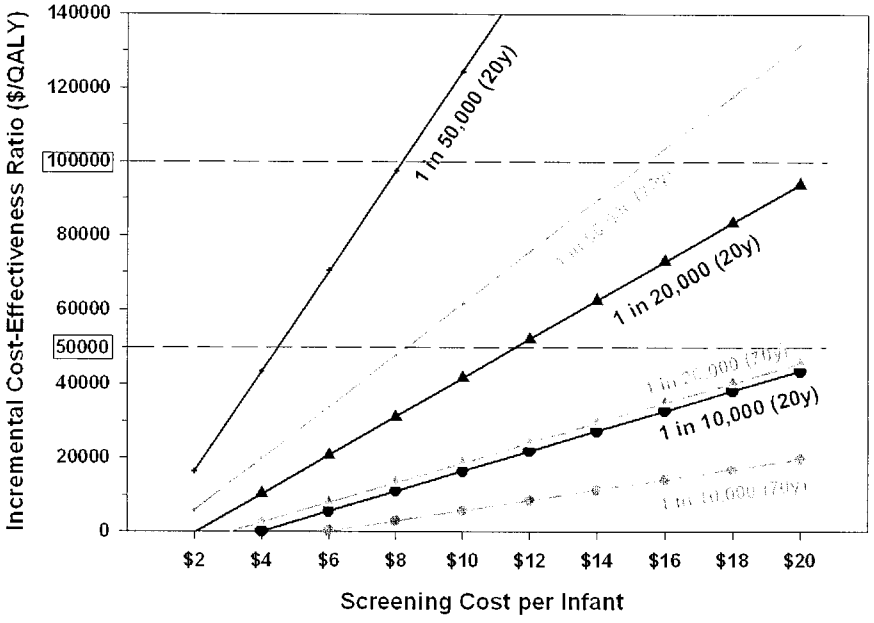

Fig 4. Cost-effectiveness by screening cost, MCADD prevalence, and time horizon.

the cost per test was $4.48 and for the 70-year horizon when it was $8.35. At the 70-year horizon, when disease frequency was >1 in 20 000, we found no test cost that caused the ratio to exceed $50 000/QALY.

Results of our 2-way sensitivity analyses for the screening test's sensitivity and specificity indicated that when the sensitivity dropped to 0.975 and specificity dropped to 0.995, the point estimate for the 20-year cost-effectiveness ratio reached $50 000/QALY; however, when the lower bounds were used for the estimates of both sensitivity and specificity, the $100 000 threshold was not exceeded. For the 70-year horizon, there were no values for test diagnostics that resulted in a ratio estimate >$50 000/QALY.

DISCUSSION

Model Predictions

Our results indicate that instituting universal newborn screening for MCADD can be achieved at an incremental cost of $5600 per QALY saved, or $11 000 per life-year saved, over a 20-year horizon and is therefore a highly cost-effective intervention.[47–62] The case for screening is further strengthened when the incremental ratio over a 70-year horizon is considered, as the respective ratios are $100 and $300. Probabilistic sensitivity analysis yielded 95% CIs for the estimated incremental cost-effectiveness ratios, with upper limits that equaled $17 100/QALY ($33 800/life-year) for the 20-year horizon and $6900/QALY ($13 000/life-year) for the 70-year ho-

rizon. The lower values of the intervals were negative, indicating that screening may be both health improving and cost saving. It is important to note that we capture this possibility although our model was biased away from screening. The critical parameters of the screening decision, such as MCADD prevalence and asymptomatic rate, diagnostic test statistics, screening costs, treatment costs, and QALY ranges, were either derived from primary data sources or surmised using conservative estimates and/or expert opinion. Sensitivity analyses demonstrated that potential thresholds were generally not exceeded when model inputs were varied across their plausible ranges, indicating that the model is stable, that the results are driven by the collective benefit of increased survival and decreased morbidity, and that universal newborn screening for MCADD is almost always cost-effective compared with not screening.

Comparison With Other Studies

Researchers in the United Kingdom, as part of an assessment of newborn screening for many IEMs, estimated the cost-effectiveness of screening for MCADD to be $100 (updated to 2001 USD) with 15 years of treatment.[4] Two more recent studies have centered on the health economics of MS/MS screening. Schoen et al[62] performed an economic evaluation of MS/MS for newborn screening for all IEMs using cost data from a cohort of 32 000 screened infants who received care through a large health maintenance organization. Although the authors achieved favorable ratios to support the screening decision, they made broad assumptions about the combined natural history of varied metabolic disorders, and none of the infants had a diagnosis of MCADD. Another report examined MS/MS screening for MCADD in the Wisconsin Newborn Screening Panel and concluded that screening for MCADD by MS/MS is cost-effective.[33] This report's authors used combined secondary data sources and assumed that MS/MS was not already in place because Wisconsin uses fluorometric methods for PKU screening. Our work differs from others in that it is based on actual MCADD patient experiences, incorporates robust simulation modeling with statistical analyses of the results, and provides an adjustable resource for other investigators.

Decision modeling techniques have been used to evaluate screening programs for conditions such as sickle cell anemia,[50,51] hearing loss,[59–61] and interventions in early life.[48] Caring for premature infants (0.5–1.0 kg) in the neonatal intensive care unit costs $53 400/QALY (updated to 2001 USD),[48] and the cost-utility ratio of cochlear implantation in infants with hearing impairment is <$10 000/QALY.[61] In addition, newborn universal screening for sickle cell disease compared with not screening costs $13 000/life-year,[50] and screening for sickle cell disease is mandated in 44 states (go to http://genes-r-us.uthscsa.edu/resources/newborn/screenstatus.htm).

Most studies examining the health economics of PKU have focused on cost per case detected, the benefit-cost ratio, and the net benefit of screening.[63] Our projection of the total cost per case of MCADD detected and treated is $74 200, which compares very favorably to PKU, which has been estimated by price standardization methods to range between approximately $66 400 and $238 200 (updated to 2001 USD).[63] One older study did consider the cost-utility of screening for PKU: Bush et al[49] estimated it to be $13 200 (updated to 2001 USD) per QALY—a value greater than our estimates of screening for MCADD. Although the validity of direct comparisons with other accepted interventions is dependent on using similar methodology and quantifying outcomes in a standard manner, the metrics that we used to assess the impact of screening for MCADD as compared with other routine neonatal and pediatric interventions indicates that it compares favorably, regardless of the exact comparator.

Limitations

Our calculations of the true cost-effectiveness ratio for universal screening for MCADD are likely to be upper-end estimates. To determine whether the screening strategy was robustly cost-effective, we were liberal in estimating costs associated with the screening strategy and conservative in estimating costs associated with the alternative. By not incorporating lost productivity costs as a result of MCADD in our cost/life-year ratio, we most likely biased our model against screening. In addition, we accounted for disutility from a false-positive report through sensitivity analysis and found the model predictions robust. Finally, we did not assume that all (unscreened) individuals with MCADD would be symptomatic and ultimately be diagnosed or die; instead, we modeled a large proportion to be entirely asymptomatic over a lifetime, which would serve only to reduce the incremental differences in decision strategies.

Other limitations relate to the underlying data such as treatment costs and patient sample, test diagnostics, utilities, and the estimate for MCADD prevalence. Treatment costs were estimated on the basis of the treatment algorithm at Children's Hospital of Philadelphia, and the MS/MS test diagnostics that we used from Neo Gen Screening Inc may not be fully representative of other laboratory experiences. Also, instead of directly eliciting patient or parent-proxied preferences for health states, we relied on previously published studies to derive reasonable utility estimates for the clinical scenarios, a limitation that we then tested by analyzing the entire utility range of 0 to 1 in sensitivity analysis. Because asymptomatic MCADD mortality statistics have not been longitudinally described and risks for adults with MCADD have not been defined,[26,64] we may also have underestimated mortality in the base-case. MCADD frequency has been reported in several studies and seems to vary between states, countries, and ethnic groups.[65] Our estimate for this value was derived from the cumulative screening of infants in a variety of states, and in populations in which MCADD is extremely rare, such as in Japan, the optimal screening decision may change with a higher screening cost than what we estimated (Fig 4).

Implications and Future Directions

The phenotypes of MCADD and other disorders that are detectable by MS/MS screening have not been fully elucidated.[66] We used primary and secondary data as well as expert opinion in decision and simulation modeling to characterize the influence of clinically important variables, such as asymptomatic rate and disease prevalence, on the cost-effectiveness of screening for MCADD. Future studies may aid in reducing uncertainty around critical variables. Prospective analyses, involving multiple institutions and larger numbers of patients with MCADD, other fatty acid oxidation disorders, and organic acidurias, will be needed to develop a comprehensive model to assess the cost-effectiveness and cost-utility of expanded newborn screening for all IEMs that are detectable using MS/MS technology.

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SMOKING ON THE SILVER SCREEN

"Smoking depicted in movies is a major and growing public-health problem. Despite a falling prevalence of smoking in the real world, the frequency of smoking in top-grossing movies in the USA has about doubled since 1990, when the US tobacco first promised Congress that it would stop paid product-placement in movies. Indeed the frequency of smoking in movies has returned to levels not seen since 1950, well before popular understanding that smoking was a major cause of disease and death. Concern over smoking in movies led WHO to make 'Smoke Free Film' a theme of 2003 World No Tobacco Day."

Glantz SA. Smoking in movies: a major problem and a real solution. *BMJ*. 2003;326:361

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