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Cost-Benefit Analysis of Universal Tandem Mass Spectrometry for Newborn Screening

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ABSTRACT. *Objective.* To estimate potential costs and benefits of routinely using tandem mass spectrometry (MS/MS) to screen newborns for inborn errors of metabolism.

Method. Analysis of costs and benefits resulting from use of MS/MS in screening of 32 000 newborn infants using data from the Kaiser Permanente Medical Care Program of Northern California plus other published data.

Setting. A large health maintenance organization.

Results. In the base scenario, the cost per quality-adjusted life year saved by MS/MS screening was \$5827; in the least favorable scenario, this cost was \$11 419, and in the most favorable scenario, \$736.

Conclusion. Costs per quality-adjusted life year saved by MS/MS screening for inborn errors of metabolism compare favorably with other mass screening programs, including those for breast and prostate cancer. *Pediatrics* 2002;110:781–786; *costs and cost analysis, homocystinuria, maple syrup urine disease, metabolism, inborn errors, neonatal screening, spectrum analysis, mass.*

ABBREVIATIONS. MS/MS, tandem mass spectrometry; IEM, inborn errors of metabolism; NBS, newborn screening; KP, Kaiser Permanente; PKU, phenylketonuria; MSUD, maple syrup urine disease; MMA, methylmalonic acidemia; PPA, propionic acidemia; MCAD, medium-chain acyl-CoA dehydrogenase deficiency; QALY, quality-adjusted years of life.

Tandem mass spectrometry (MS/MS) is being used increasingly in early diagnosis of inborn errors of metabolism (IEM) in the hope of avoiding the severe developmental delay, acute illness, and death that may result from these diseases.^{1–13} Although >30 types of IEM can be diagnosed with the aid of MS/MS, its universal, routine use is controversial because of the rarity of these disorders, questions of treatability and outcome, and concern about high costs.^{11,14–20} With rapid expansion of universal newborn MS/MS screening in an increasing number of states,^{1,3–5} the economic impact of this laboratory technology on newborn screening (NBS) becomes relevant. Here, we estimate the po-

tential impact on costs and benefits of MS/MS in NBS in a large health maintenance organization.

METHODS

Sources of Cost Data

For cost analysis, we used NBS cost data from Kaiser Permanente (KP) of Northern California, a health maintenance organization region that serves >3 million members and at which 32 000 infants are delivered each year; reference cost data from outside sources; and estimated costs incurred in early versus late diagnosis of IEM. In line with California policy, NBS tests are performed in the regional KP laboratory using standardized equipment provided by the state. The current California NBS program tests for congenital hypothyroidism, phenylketonuria (PKU), galactosemia and hemoglobinopathies. Although PKU can be diagnosed by MS/MS along with many inborn metabolic disorders, the other conditions (congenital hypothyroidism, galactosemia, hemoglobinopathies) can not. To estimate the costs of early and late treatment as well as rates of false-positive test results, we used previously published data^{4–7,14,18,20} in addition to KP internal data.

Internal cost data were obtained from the KP Cost Management Information System, an automated system, which integrates KP's Northern California Regional Medical Utilization database and the KP General Accounting Ledger and itemizes fully allocated costs by department, by medical center, by patient, and by procedure. Cost Management Information System also uses data from a separate referral database of medical utilization at non-KP facilities.

In addition, cost estimates for treatment and follow-up were based on information from the KP Regional Metabolic Clinic, which currently manages metabolic disorders in >200 children, including 7 children with maple syrup urine disease (MSUD), 8 with methylmalonic acidemia (MMA) or propionic acidemia (PPA), and 96 with PKU. In addition to these internal data, our analysis included amounts of required follow-up care estimated by our 4 metabolic geneticists on the basis of their experience.

Lifetime Discounted Treatment Cost

"Lifetime discounted treatment cost" was considered in the calculations because in screening programs money is spent today for future benefits. In general, gains of all types, including health gains, are preferred to occur earlier rather than later, and a discount factor is applied to account for this time preference. We used a 3% lifetime discounted cost, a commonly used figure. Failure to discount could encourage policymakers to delay implementing health programs indefinitely.^{21,22}

Estimated Disease Incidence and Rates of False-Positive Test Results

Estimated treatment costs included 7 general categories of IEM, for which the following incidence rates were assumed^{3,4,18,19}: MSUD, 1:20 000; medium-chain acyl-CoA dehydrogenase deficiency (MCAD) and other disorders of fatty acid oxidation, 1:10 000; glutaric aciduria, type I, 1:20 000; MMA/PPA (included here as examples of organic acid disorders), 1:50 000; urea cycle disorders, 1:50 000; homocystinuria, 1:200 000; PKU, 1:15 000.

For all these disorders except PKU, we assumed a false-positive: true-positive ratio of 25:1. This assumption was made on the basis of our experience and published reports of actual and estimated false-positive rates ranging from 5:1 to 50:1.^{3,4,18,19} With

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added experience, the false-positive-to-true-positive ratio may decrease, and the decrease in false-positive tests would increase the cost benefit of the test. For PKU, we assumed a false-positive: true-positive ratio similar to the 8:1 ratio currently achieved in California with the fluorometric method; the 600 000 NBS tests conducted at KP from 1978 through 2000 showed a false-positive: true-positive ratio of 14:1 for PKU and 8:1 for congenital hypothyroidism.

To estimate number of quality-adjusted life years (QALY) saved by prevention of neurologic deficit, we used published data from studies of other disorders that cause neurologic defects.^{23–26} The subject of these studies were adults; no comparable information is available in children. Costs of MS/MS analysis were based on values obtained from US States (eg, North Carolina, Wisconsin, and Pennsylvania) currently using MS/MS^{3,4,12} and on charges obtained from commercial laboratories. Costs for false-positive test results were estimated using internal KP data for existing NBS programs. Sensitivity analysis was used to estimate effects of changes in base assumptions. Various ranges of test costs, treatment costs, rates and costs of false-positive test results, mortality rates, and adjustments for QALY were used. In addition to our base set of assumptions, we created 2 alternative sets of assumptions: 1 set was based on a scenario least favorable to MS/MS screening, and another set was based on a scenario most favorable to MS/MS. The analysis did not include cost of special education programs or cost of labor value gained by preventing neurologic deficit.

Estimated Base Costs Incurred and Saved as a Result of Early Diagnosis

The base laboratory cost for MS/MS was estimated at \$15 per test and included the costs of prompt specimen transportation, processing, and interpretation of results. The State of California currently mandates that blood samples taken for NBS be drawn when the newborn is discharged from the hospital but no sooner than age 12 hours and no later than age 6 days (most newborns are discharged from the hospital at age 24–72 hours). Because presymptomatic treatment is particularly important in most IEM, eg, MSUD or urea cycle defects,^{11,27} quick diagnosis and management are necessary and require early collection of specimens (ie, before age 48 hours), rapid turnaround time, and continuous availability of metabolic specialists and emergency services. In addition, laboratories should perform MS/MS 7 days per week and also have a replacement machine readily available.

Infants with MSUD and other IEM may become symptomatic within the first week of life and may require hospitalization,¹¹ usually in neonatal intensive care units at a cost which often exceeds \$35 000; infants whose metabolic disease is detected presymptomatically by MS/MS require shorter, less intensive hospital stays. For analysis of the base scenario, we assumed an initial treatment cost savings of \$25 000 for presymptomatic diagnosis versus diagnosis made after symptoms manifested.

Costs of treatment received during the first 5 years of life were estimated on the basis of experience at KP, where 3 major cost factors apply: 1) special tests are done repeatedly for each patient; 2) patients must be diagnosed and treated in costly multispecialty clinics, such as the KP Regional Metabolic Clinic; and 3) disease-specific formulas usually required during treatment cost about \$10 000 annually. Moreover, particularly during the first 5 years of life, additional care is needed for children with IEM detected after symptoms manifest. This additional care is needed because these children have greater global developmental delay as well as greater susceptibility to infection. These factors increase outpatient costs as well as the likelihood of both hospital admission and care in the intensive care unit. We assumed an annual hospital admission rate of 25% for patients aged ≤5 years with IEM diagnosed late; we assumed an annual admission rate of 7.5% for patients with IEM diagnosed before symptoms manifested.

For analysis of the base scenario, we estimated long-term treatment costs by assuming that among patients aged >5 years, the annual hospital admission rate was 9% if IEM were diagnosed late and was 3% if IEM were detected early.

In addition, we assumed a 20-year difference in life expectancy between affected patients diagnosed late (life expectancy of 45 years) and those diagnosed early by screening (life expectancy of 65 years). With regard to sensitivity testing of IEM detection among affected patients diagnosed early versus late, we assumed

a 15-year difference in life expectancy between groups of patients diagnosed in the least favorable scenario (ie, least sensitive IEM detection) and a 25-year difference in life expectancy between groups of patients diagnosed in the most favorable scenario.

Our analysis included a small cost offset for PKU, because use of total mass spectrometry will eliminate the current need for PKU laboratory testing.

Estimated Costs of False-Positive Test Results

Because of the immediate response required to treat IEM diagnosed by MS/MS, false-positive test results are costly. The diagnosis necessitates immediate response by a genetics nurse-coordinator (\$100), a visit to an urgent care clinic (\$110), several laboratory tests (costing as much as \$600 total), and, in some cases, consultation with a geneticist (\$200). Some false-positive test results engender a visit to the emergency department (\$200), admission to the hospital for an overnight stay (\$2000), or both. On the basis of these estimated costs, each disorder was assigned a cost of \$1000 for every false-positive test result. (Costs associated with various disorders differ slightly from one another because of the different laboratory tests required and because of different response times, but these cost differences are relatively small.) Because MCAD usually requires no immediate intervention, the cost of each false-positive test result was set at \$200 to cover costs of conducting repeat laboratory tests and tracking results of these tests.

Quantifying Changes in Morbidity and Quality of Life

The effect of early, presymptomatic diagnosis of most IEM will be primarily on quality of life rather than mortality. To account for this effect, we adjusted mortality for quality of life. Estimates of utility level of patients with serious neurologic defects range from 0.15 to 0.30 (normal value of 1). Early detection of IEM was estimated to result in the addition of between 0.70 and 0.80 QALY. MCAD was assumed to rarely cause developmental effects and just the possibility of sudden infant death syndrome.^{3–5,8–11,27} Although cases of undiagnosed MCAD are known to cause severe hypoglycemia, no health plan members have been diagnosed with MCAD in the KP Northern California system. (The rationale for the MCAD assumption is described in the “Discussion” section.)

RESULTS

Results are presented in Tables 1 through 5. Costs are listed both per screened infant and for a cohort of 100 000 births. Costs of false-positive test results range from \$1.21 to \$12.25 per infant screened, depending on rate of false-positive test results (Table 5). Early diagnosis resulted in lifetime treatment cost savings ranging from \$4.86 to \$5.98 per test performed (Table 5). Most savings in treatment costs in early diagnosed cases were realized within the first 5 years of life, because of decreased hospitalization costs (Table 5). The biggest cost factor was initial laboratory cost, estimated at \$15 in the base scenario with a range of \$7 to \$20 per test. Because of the reduced mortality rates and improved QALY resulting from early diagnosis, each patient screened gained a mean of 0.0026 QALY (Table 5). The cost per QALY was \$5827 in the base scenario.

In the unfavorable scenario—ie, higher laboratory costs, more false-positive test results, and smaller effects on rates of mortality and morbidity—cost per QALY was \$11 419; in the favorable scenario, cost per quality-adjusted year of life was \$736. In the unfavorable scenario, cost of false-positive test results was even more important: Mean per-test cost of false-positive test results was \$12.25. Assumptions regarding the value of early detection in relation to QALY were also important.

TABLE 1. Costs of Treatment and of False-Positive Results of MS/MS in Base Scenario

Condition	Incidence*	No. of False-Positive Test Results*	Cost of False-Positive Test Results*	Lifetime Discounted Treatment Cost			Treatment Cost Savings*
				IEM Detected Early	IEM Detected Late	Difference	
MSUD	5	125	\$125 000	\$51 489	\$8938	\$42 551	\$212 755
MCAD and other disorders of fatty acid oxidation	10	250	\$250 000	\$0	\$0	\$0	\$0
Glutaric aciduria, type I	5	125	\$125 000	\$51 489	\$8938	\$42 551	\$212 755
MMA/PPA	2	50	\$50 000	\$51 489	\$8938	\$42 551	\$85 102
Urea cycle disorders	2	50	\$50 000	\$51 489	\$8938	\$42 551	\$85 102
Homocystinurea	0.5	12.5	\$12 500	\$51 489	\$8938	\$42 551	\$21 276

* Per 100 000 patients.

TABLE 2. Potential Life Expectancy (in Years) and QALY in Base Scenario

Condition	Life Expectancy		Total Undiscounted QALY		Total Discounted QALY		Difference
	IEM Detected Early	IEM Detected Late	IEM Detected Early	IEM Detected Late	IEM Detected Early	IEM Detected Late	
MSUD	65	45	62	11	26	6	20
MCAD and other disorders of fatty acid oxidation	70	69	70	69	29	29	0.1
Glutaric aciduria, type I	65	45	62	11	26	6	20
MMA or PPA	65	45	62	11	26	6	20
Urea cycle disorders	65	45	62	11	26	6	20
Homocystinurea	65	45	62	11	26	6	20

TABLE 3. Assumptions Underlying Analysis of Annual Cost for NBS with MS/MS Under 3 Clinical Scenarios, Each With Clinic Cost of \$1500

	Base Scenario		Unfavorable Scenario		Favorable Scenario	
	IEM Detected Early	IEM Detected Late	IEM Detected Early	IEM Detected Late	IEM Detected Early	IEM Detected Late
Cost of inpatient stay	\$4000	\$8000	\$4000	\$8000	\$4000	\$8000
Percentage of patients aged ≤5 y staying >5 d in hospital	25.0	75.0	33.3	66.6	20.0	80.0
Percentage of patients aged >5 y staying >5 d in hospital)	3.0	9.0	3.0	6.0	2.5	10.0
No. of patients with <5 outpatient visits	2	3	2	3	2	3
No. of patients with >5 outpatient visits	1	2	1	2	1	2
Annual cost of formula for children aged 0-4 y with IEM	\$10 000		\$10 000		\$10 000	
Annual cost of special diet for patients aged ≥5 y with IEM	\$2500		\$2500		\$2500	

TABLE 4. Five-Year Discounted Treatment Costs per Case for Patients Aged ≤5 Years With IEM

Condition	IEM Detected Early	IEM Detected Late	Difference
MSUD	\$64 116	\$118 884	\$54 768
MCAD and other disorders of fatty acid oxidation	\$0	\$0	\$0
Glutaric aciduria, type I	\$64 116	\$93 884	\$29 768
MMA or PPA	\$64 116	\$93 884	\$29 768
Urea cycle disorders	\$64 116	\$93 884	\$29 768
Homocystinurea	\$64 116	\$93 884	\$29 768
Mean 5-y treatment cost savings per test: \$5.19			

DISCUSSION

Our analysis showed that the cost of MS/MS per QALY compares favorably with other screening methods as well as with other types of treatment. Prostate cancer screening has been estimated to cost between \$8400 and \$23 100 per QALY, whereas

breast cancer screening has been estimated to cost \$5815 among patients of all ages.²⁸ Breast cancer screening for women under 50 years old has been estimated to cost \$232 000 per QALY.²⁸ Semiannual screening for retinopathy in high-risk patients with type 2 diabetes has an estimated cost of \$49 760 per

TABLE 5. Summarized Results of Lifetime Cost-Benefit Analysis for MS/MS Screening Under 3 Scenarios

Costs and Benefits per Test	Base Scenario		Unfavorable Scenario		Favorable Scenario	
	Per Patient	Per 100 000 Patients	Per Patient	Per 100 000 Patients	Per Patient	Per 100 000 Patients
Cost of false-positive test results	\$6.13	\$612 500	\$12.25	\$1 225 000	\$1.21	\$121 000
Laboratory and collection costs	\$15.00	\$1 500 000	\$20.00	\$2 000 000	\$7.00	\$700 000
Total immediate costs	\$21.04	\$2 112 500	\$32.21	\$3 225 000	\$8.07	\$821 000
Treatment savings	\$5.64	\$563 809	\$4.86	\$485 840	\$5.98	\$598 479
Net cost	\$15.49	\$1 548 691	\$27.39	\$2 739 160	\$2.23	\$222 521
Quality-adjusted years of life gained	0.0026	264.29	0.0024	239.56	0.0028	283.25
Cost per QALY	\$5 827		\$11 419		\$736	

QALY.²⁹ Beta-interferon treatment for hepatitis C has been estimated to cost \$7500 per QALY.³⁰ Equipping commercial aircraft with onboard automatic external defibrillators to improve passengers' rate of survival after cardiac arrest costs an estimated \$50 000 per QALY.³¹

Medical cost savings resulting from early diagnosis occurs primarily in the first 5 years of life as a result of decreased ICU and hospital costs. Even patients with IEM detected early will require expensive formula and dietary supplements as well as increased outpatient care throughout life (Table 4). For patients aged >5 years, differential costs are less because rates of hospitalization in both groups decrease. Thus, the reduced hospital costs early in life are slightly offset by cost incurred by expected increased longevity. Because early detection enables patients to live longer, these long-term follow-up costs can rise when screening is introduced.

There is evidence that diagnosis of MSUD between the third and seventh days of life, followed by effective treatment, reverses intoxication within 24 to 48 hours and decreases the risk of brain damage.³² If MSUD is subsequently well managed, these infants will grow and develop normally. If the diagnosis is not made until the infant becomes symptomatic, often at 5 to 21 days of age, prolonged hospitalizations and intensive care are required, and there is increased risk of poor developmental outcomes.^{33–36}

MCAD requires special consideration as the most common of the IEM: Its estimated prevalence is 1:10 000 to 1:20 000.^{1,4–11} Evidence indicates that most people born with MCAD do not have serious sequelae.^{8–10} A study of 20 patients with MCAD in New South Wales⁸ included 5 patients (25%) who died at age 3 days to 30 months and 2 patients (10%) who had serious, life-threatening episodes after diagnosis. The 15 survivors included 1 (5%) who had severe neurologic disabilities and 4 (20%), aged between 9 and 17 years, who had mild intellectual handicap. However, the patients in that series⁸ represent only 22% of all persons born with MCAD; thus, assuming a 1:20 000 prevalence of MCAD, death rate is 5%; rate of severe handicap, 1%; and rate of mild handicap, 4%. Data from recent US screening programs suggest MCAD prevalence of 1:10 000^{1,4–7,11}; combining this incidence with the data of Wilcken et al⁸ yields a death rate of 2.5%, 0.5% rate of severe handicap, and 2% rate of mild

handicap—a 5% rate of adverse outcome among infants and children born with MCAD. Of 41 MCAD cases analyzed by Wilson et al,⁹ nearly half the patients had been admitted to the hospital because of symptoms suggesting MCAD, and severe encephalopathy later developed in 2 (5%), but no deaths or “appreciable morbidity”⁹ occurred. A retrospective study¹⁰ reported that 19% of 120 MCAD patients died and that “unexpected morbidity”¹⁰ occurred in the survivors. But, as in the other 2 studies,^{8,9} affected patients came to the authors' attention after treatment and not prospectively through NBS. Our experience at KP confirms the likelihood that most patients with MCAD do not have symptoms of the disease and therefore would not be identified in the absence of a screening program. In our large metabolic clinics, we have treated >200 patients with IEM, including 97 with PKU—and MCAD is at least as prevalent as PKU in the general population. Yet we currently have no patients with MCAD, although we are treating children affected with MSUD, MMA/PPA, and other IEM that are detected much less frequently than MCAD in screening programs.^{1,4–11} Medical management of MCAD is also less complex and costly than for other IEM; hallmarks of treatment for MCAD include frequent feeding (to avoid hypoglycemia), adherence to a low-fat diet, and administration of carnitine. We believe that the infrequency of symptoms and sequelae and the low cost of treatment justify our assumption that the economic impact of MCAD is smaller than for more uncommon IEM with more severe sequelae. If subsequent prospective studies of total mass spectrometry screening programs show that rates of death and morbidity are higher than our conservative estimates of 3% to 7%, such findings would substantially decrease the costs of QALY and more strongly favor MS/MS screening.

The rate of false-positive test results is an important cost factor in using MS/MS for NBS. In some current screening programs, the ratio of false-positive:true-positive test results has been higher than 50:1.⁴ We assumed a smaller ratio, 25:1, for analysis of the base scenario. A low rate of false-positive test results can be achieved only if 3 conditions are met: 1) MS/MS is used to screen for prespecified abnormalities only; 2) MS/MS screening is not used to evaluate all substances ascertainable by this highly sensitive technology; and 3) positive test results are determined according to a reasonable, preset cutoff point. For those MS/MS programs not limiting their

scope of diagnosis, false-positive rates and costs will probably be appreciably higher.

Other pediatric screening programs^{19,37–42} have shown that a false-positive test result can have a long-term, detrimental effect on the parents, may influence the way parents view their offspring, and may lead to an overprotective attitude toward the child. Despite assurances to the contrary and despite normal results of follow-up tests, some parents feel that something must have been wrong with the child for the test to have been initially positive. Thus, maintaining a low rate of false-positive test results is important from a clinical and sociologic viewpoint as well as from an economic standpoint, and this importance should be considered in a decision to implement screening. Although screening programs using MS/MS may seem to yield higher rates of false-positive test results than do many other screening programs, data reported by some large MS/MS screening studies have not specified rates of false-positive test results.^{1,3,5,7} Failing to consider the costs of false-positive tests ignores an important cost factor and biases these programs in favor of screening.

In addition to increasing laboratory costs and causing parental anxiety, false-positive test results can generate a cascade of costly clinical events, including emergency department visits, hospital admissions, additional definitive laboratory studies, and use of on-call medical personnel (including metabolic specialists). Cost analyses of screening programs are often limited to laboratory expenses and some treatment costs; the analyses generally ignore other costs, ie, costs of confirming the diagnosis, tracking test results, counseling, clinical visits, and treatment follow-up. Instituting a new screening procedure is best accomplished not just by adding advanced laboratory technology but by introducing a total tracking and follow-up program. Failure to realize this fact may result in grossly underestimated costs. To emphasize the complexity and importance of a total screening program, we have developed an acronym for the multiple steps involved. We call these multiple steps the “11 Ts” of screening: 1) technology (equipment), 2) training (personnel), 3) taking (specimen collection), 4) transportation of specimens, 5) testing, 6) telling (reporting test results), 7) tracking (confirming results, false-positive), 8) teaching (counseling subjects and providers), 9) treating, 10) tracking (long-term follow-up, outcomes), 11) totaling (sum of all costs). Others have recognized some of these limitations.⁴³

Because severe clinical manifestations of many IEM (eg, MSUD, urea cycle disorders) may occur in the immediate neonatal period, a highly coordinated screening program with fast laboratory turnaround time and rapid clinical intervention by highly trained professionals is required. A sophisticated tracking program is necessary for follow-up and to guarantee patients' compliance with prescribed treatment regimens. These rapid-response screening and tracking programs are expensive but are rarely included in cost analysis studies. Implementing such a highly coordinated system may be difficult under certain circumstances, such as in rural areas and in pro-

grams without close laboratory or clinical cooperation. Most patients with IEM incur high dietary costs throughout life, beginning with formula required in infancy and early childhood and continuing with specially formulated foods required later in life. In recognition of these dietary requirements, the State of California—which previously had mandated that medical insurance for patients with IEM cover only the cost of formula—recently added the requirement that the cost of special foods be covered in older persons with IEM.⁴⁴

Study Limitations

Our search of the biomedical literature on MS/MS screening did not show reported rates of false-positive test results similar to the rates used in our analysis. Indeed, some evidence⁴ suggests that rates of false-positive test results obtained by using MS/MS will be much higher than the 14:1 ratio we found for NBS tests conducted at KP; however, data reported in most large MS/MS studies do not include rates of false-positive test results.^{1,3,5,7} Ratio of false-positive: true-positive test results in 1 US state fluctuated between 8:1, 41:1, and 9:1 at different times during the screening program.⁴

Because the IEM we considered are so rare and because early diagnosis and longitudinal studies of patients with these conditions are even rarer, several of our assumptions relating to cost, morbidity rates, and mortality rates were based either on a small number of published observations^{16–20,27} or on projections made by KP metabolic geneticists from their own clinical experience. Moreover, until the past 2 decades, IEM often proved fatal during infancy or early childhood; therefore, long-term survival rates among patients with these disorders are not yet known.^{16,17}

CONCLUSION

Whether detected presymptomatically (ie, by screening) or after symptoms manifest, IEM in infants and children is expensive to manage. Our finding that the cost of MS/MS screening per quality-adjusted year of life compares favorably with costs of other accepted screening procedures supports a policy of encouraging MS/MS screening. However, when a program of NBS using MS/MS is financed, the calculations should consider total expenses, including costs not only of equipment and analysis but also costs of training, personnel, tracking test results, counseling parents, supplying special diets and specialty care, and clinical follow-up.

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